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Evaluation Report ERC2011-04

Ipconazole

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Overview

Registration Decision for Compound Ipconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Ipconazole Technical Fungicide and Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide, containing the technical grade active ingredient ipconazole, to protect against seedling and soil-borne diseases on small grain cereals and corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the registrant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Ipconazole Technical Fungicide and Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management Portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Ipconazole?

Ipconazole is a triazole fungicide used to control various fungi species. This active ingredient is used as a seed treatment on small grain cereals and corn to control smuts, bunts, leaf stripe and seed and seedling diseases caused by *Fusarium* spp., *Cochliobolus sativus*, *Rhizoctonia solani*, *Rhizopus* spp., *Cladosporium* spp., *Aspergillus* spp., and *Penicillium* spp. Ipconazole is classified as a Group 3 fungicide that inhibits sterol biosynthesis in fungi.

Health Considerations

Can Approved Uses of Ipconazole Affect Human Health?

Ipconazole is unlikely to affect your health when used according to label directions.

Potential exposure to ipconazole may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when ipconazole products are used according to label directions.

Ipconazole was moderately acutely toxic by the oral route, slightly acutely toxic by the inhalation route and mildly irritating to the eyes. Consequently, the hazard statement "WARNING POISON - EYE IRRITANT" was required on the label.

The end-use products, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide were of low acute toxicity. Consequently, no hazard statements were required on the product labels.

Ipconazole did not cause cancer in mice and rats, and was not genotoxic. However, there was some concern regarding the dose adequacy to assess cancer in the rat. There was also no indication that ipconazole caused damage to the nervous system. The first signs of toxicity in animals given daily doses of ipconazole over longer periods of time were effects on the non-glandular stomach (also known as the forestomach) in mice and rats, the eyes (lens), prostate, kidney and thymus in dogs and the liver in all species tested. The effects observed in the non-glandular stomach of rodents are not toxicologically relevant to humans. The female reproductive system (ovaries), endocrine organs and immune system were targeted at higher dose levels.

When ipconazole was given to pregnant animals, effects on the developing foetus were observed at doses that were toxic to the mother. However, since effects in the foetus were of a more severe nature than those seen in the mother, the foetus is considered more sensitive to ipconazole than the adult animal.

The risk assessment protects against the above effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. Additional factors were applied to the risk assessment to account for the concerns surrounding the adequacy of dosing in the rat-cancer study.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 3–5 yrs, the subpopulation which would ingest the most ipconazole relative to body weight, are expected to be exposed to less than 1.7% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from ipconazole is not of concern for all population sub-groups. There is no associated cancer risk from the use of ipconazole on corn (field, sweet and pop), wheat, barley, rye, triticale and oats. An aggregate (food plus water) dietary intake estimate for females 13–49 years old used less than 0.25% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* (FDA) prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the *Pest Control Products Act* (PCPA). Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using ipconazole on wheat, corn, barley, soybean and peanut were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Report.

Occupational Risks From Handling Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide

Occupational risks are not of concern when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide are used according to the label directions, which include protective measures.

Workers mixing and loading Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide, or treating seed, as well as workers handling and planting freshly treated seed, can come in direct skin contact with the active ingredient, ipconazole, in these products. Therefore, the labels specify that anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves. Closed mixing/loading equipment is required and closed cab tractors must be used for planting seed treated with Rancona Apex Fungicide. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What happens when ipconazole and related end-use products are introduced into the environment?

Environmental risks are negligible when Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide are used according to label directions, which include precautionary label statements concerning seed burial and cleanup of spilled seed.

Ipconazole can enter the environment by dislodging from treated seed surfaces during and after seeding. Ipconazole is persistent in the environment, with soil biodegradation being the primary route of transformation. Ipconazole has low mobility in soil and has low potential to leach to groundwater. Ipconazole is not expected to reach surface waters in any appreciable amounts under the current use pattern, as exposure of surface waters through soil runoff and leaching is expected to be minimal. Some toxicity occurred to laboratory animals exposed to ipconazole; however, the primary environmental risk under the current use pattern is to birds and mammals that may consume treated seed. This risk was determined to be negligible if label statements regarding burial and cleanup of spilled seed are followed. Risk to other terrestrial and aquatic organisms, and non-target plants is negligible based on low potential for exposure to these groups.

Value Considerations

What Is the Value of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide?

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are seed treatments for use on field corn, sweet corn and popcorn to provide protection against seed, seedling and soil-borne diseases. Rancona Apex Fungicide is a reduced-risk fungicide seed treatment used to control diseases on cereals including wheat, barley, oats, rye and triticale.

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are alternatives to several older chemicals currently used as corn fungicide seed treatments. As seed treatments, the rate per hectare of all of these products is low and application to the seed reduces exposure to non-target organisms compared to foliar pesticide applications. Rancona Apex Fungicide is a liquid seed treatment with a low concentration of active ingredient and is effective at low rates. Cereal diseases can be adequately controlled using Rancona Apex Fungicide.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the labels of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide on the skin or through inhalation of dusts, anyone handling Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, contaminated equipment, or corn seed treated with these products, must wear long pants, a long-sleeved shirt and chemical-resistant gloves. The labels also require that closed mixing/loading equipment be used. For Rancona Apex Fungicide, workers handling the product, contaminated equipment or cereal seed treated with this product, must wear long-sleeved coveralls over normal work clothing and chemical-resistant gloves. Closed mixing/loading equipment is required and closed-cab tractors must be used for planting seed treated with Rancona Apex Fungicide.

Environment

The use of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide may pose a risk to birds and mammals that consume significant amounts of treated seed. Precautionary label statements will be added to the product labels to identify and mitigate this risk (namely, burial of treated seed and cleanup of spilled, treated seed).

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the registrant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report and in the section 12 Notice associated with these conditional registrations. The registrant must submit the following information within the time frames indicated.

Human Health

- A new rat cancer study at higher doses.
- Hormonal measurements in rats after at least 28-days of treatment.
- Toxicology studies being requested by other regulatory authorities.
- Additional supporting data consisting of dust-off studies comparing the dust-off potential of Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide on corn, and oats treated with Rancona Apex Fungicide, with that of the formulation and seed used in the surrogate studies used in the risk assessments, or an acceptable rationale, are requested
- Freezer storage stability data.
- Data must be submitted within three years of this registration.

Value

- Three small-scale field, greenhouse and/or lab (Petri plate) trials confirming that Rancona Apex Fungicide is effective in controlling post-emergence damping-off caused by *C. sativus* on wheat, barley, oats, rye and triticale are required.
- Field trials on each pathogen (one on *Fusarium* spp. and two on *R. solani*) demonstrating that Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide are effective in controlling seed rot, damping-off and seedling blight caused by soil-borne *Fusarium* spp. and seed rot and damping-off caused by *R. solani* on sweet, field, and popcorn are required.
- Data must be submitted within three years of this registration.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

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[3] As per subsection 28(1) of the *Pest Control Products Act*.

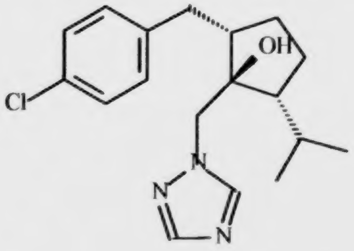
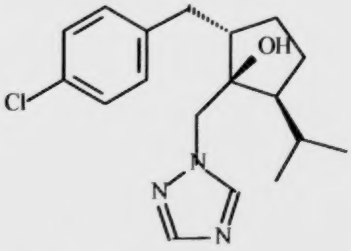
The test data cited in this Evaluation Report (namely, the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Science Evaluation

Ipconazole Technical Fungicide

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Ipconazole (ratio of cc to ct isomers is approximately 9:1)
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(1RS,2SR,5RS;1RS,2SR,5SR)-2-(4-chlorobenzyl)-5-isopropyl-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
2. Chemical Abstracts Service (CAS)	2-[(4-chlorophenyl)methyl]-5-(1-methylethyl)-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol
CAS number	125225-28-7 (unstated stereochemistry) 115850-69-6 (cc isomer) 115937-89-8 (ct isomer)
Molecular formula	$C_{18}H_{24}ClN_3O$
Molecular weight	333.9
Structural formula	 cc isomer  ct isomer
Purity of the active ingredient	97.4%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products

Technical Product—Ipconazole Technical Fungicide

Property	Result
Colour and physical state	White powder
Odour	Almond-like odour
Melting range	85.5–88.0°C
Boiling point or range	Not applicable
Density	1.18–1.26 g/cm^3
Vapour pressure at 20°C	$<5.05 \times 10^{-5}$ Pa
Henry's law constant	1.36×10^6 for ipconazole cc 7.25×10^5 for ipconazole ct
Ultraviolet (UV)-visible spectrum	A major maximum at 222 nm and a minor maximum at 268 nm; no absorbance above 300 nm.
Solubility in water at 20°C	Solvent — cc isomer (mg/L) — ct isomer(mg/L) water — 9.34 — 4.97 pH 5.0 — 9.86 — 5.79 pH 7.0 — 8.68 — 4.60 pH 9.0 — 9.13 — 4.71
Solubility in organic solvents at 20°C (g/L)	Solvent — Solubility acetone — 570 1,2-dichloroethane — 425 dichloromethane — 583 ethyl acetate — 428 heptane — 1.90 methanol — 679 n-octanol — 230 toluene — 156 xylenes — 151
n-Octanol-water partition coefficient (K_{ow})	cc isomer — Log $K_{ow} = 4.65$ ct isomer — Log $K_{ow} = 4.44$
Dissociation constant (pK_a)	Unable to determine using the spectrophotometirc method described in OPPTS 830.7370.
Stability (temperature, metal)	Ipconazole Technical Fungicide is stable in the presence of iron, aluminum, iron (II) acetate and aluminum acetate, basic for 14 days at both 20°C and 54°C.

End-Use Products—Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide

Property	Result
Colour	Beige
Odour	Very faint odour, reminiscent of latex paint
Physical state	Liquid
Formulation type	Suspension (SU)
Guarantee	450 g/L
Container material and description	HDPE bottles or drums
Density at 20°C	1.107 g/mL
pH of 1% dispersion in water	7.0–8.5
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable for 1 year under commercial storage conditions
Corrosion characteristics	No corrosion was observed during 1 year storage.
Explodability	Not explosive

End-Use Product—Rancona Apex Fungicide

Property	Result
Colour	Reddish-orange
Odour	Slightly musty odour
Physical state	Liquid
Formulation type	Solution (SN)
Guarantee	4.61 g/L
Container material and description	10 L HDPE jugs and 1000 L LDPE totes
Density at 20°C	1.0–1.1 g/mL
pH of 1% dispersion in water	7.0–9.0
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable for 1 year under commercial storage conditions
Corrosion characteristics	For HDPE bottles, no evidence of perforation, imperfection or discoloration. But for LDPE boxes, the interior has a ring of pink stain. There is no evidence of either decomposition of the product or degradation of the packaging material.
Explodability	Not explosive

1.3 Directions for Use

Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are systemic broad-spectrum fungicides with protective action. These fungicides are intended for use by commercial seed treatment applicators only and should be applied using standard commercial seed treatment equipment. An appropriate colorant must be added when these products are applied to seed. Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide should be applied to corn seed at a rate of 5.6 mL/100 kg seed for all diseases.

Rancona Apex Fungicide is a broad-spectrum, ready to use seed treatment fungicide with systemic properties. Application should take place using mechanical, slurry or mist-type on-farm or commercial seed treating equipment. Rancona Apex Fungicide should be applied to seed at a rate of 325 mL/100 kg seed for all diseases, but may be applied at 433 mL/100 kg seed on barley seed lots with high levels of true loose smut infection.

1.4 Mode of Action

Ipconazole is a Sterol Biosynthesis Inhibitor (SBI). It belongs to a major class of SBI's (demethylation inhibitors or DMI's) and is classified as a Group 3 fungicide. It acts against target fungi by inhibiting cytochrome P450-dependent C-14 demethylation in the sterol-biosynthesis pathway. Ipconazole is a systemic fungicide with high fungicidal activity against various fungi species.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Ipconazole Technical Fungicide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High-performance liquid chromatography method with mass spectrometry (HPLC-MS) was developed and proposed for data generation and enforcement purposes. This method fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. An acceptable recovery (85.6%) was obtained in soil. Method for residue analysis is summarized in Appendix I, Table 1.

2.3.1 Multiresidue Methods for Residue Analysis

Ipconazole was analyzed according to the FDA Multi-Residue Method (MRM) Test guidelines in PAM Vol. I (3rd edition, last revised 10/99). The suitability of the FDA MRM protocols to analyze for residues of ipconazole in non-fatty and fatty foods was evaluated. After following the applicable PAM I protocols, it was concluded that the FDA multi-residue methods are not suitable for residue analysis and enforcement purposes of ipconazole.

2.3.2 Methods for Residue Analysis of Plants and Plant Products

A number of high-performance liquid chromatography–electrospray ionization with tandem mass spectrometry (HPLC-MS/MS) methods were developed for the analysis of ipconazole and/or the metabolites triazolylalanine (TA), triazolylacetic acid (TAA), triazolylpyruvate (TP) and 1,2,4-triazole (1,2,4-T) in food of plant origin for data gathering (KRA/0134-01R and KRA/119-03R) and enforcement purposes (AC-3020A). All methods fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation (LOQ). A LOQ was reported as 0.01 ppm in plant products for each analyte. Acceptable recoveries (70–120%) of ipconazole and the metabolites were obtained in plant matrices. Extraction efficiency data demonstrated that the enforcement method can account for incurred residues of ipconazole and the metabolites in wheat matrices.

2.3.3 Methods for Residue Analysis of Food of Animal Origin

An enforcement method to quantitate ipconazole residues was not submitted due to the low expectation of ipconazole residues in animal matrices.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for ipconazole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product, with the exception of the cancer assessment in the rat combined chronic/carcinogenicity study.

Ipconazole is structurally similar to many other triazole compounds used as pesticides with a proposed mode of action (MOA) of inhibition of sterol 14α-demethylase and aromatase (CYP19) (Zarn et al., 2003). In mammals, sterol 14α-demethylase converts lanosterol into meiosis-activating sterols, while aromatase converts androgens into corresponding estrogens. Inhibition of these processes will ultimately lead to a disruption in cholesterol biosynthesis and steroidogenesis, respectively. The fungicidal MOA involves disruption of fungal cell membranes and walls through inhibition of fungal lanosterol-14α-demethylase.

Ipconazole was of moderate acute toxicity by the oral route in mice and rats. It was of low dermal toxicity and slightly acutely toxic by the inhalation route in rats. Ipconazole was non-irritating to the skin and mildly irritating to the eyes of rabbits, and was not a dermal sensitizer in guinea pigs according to the Maximization method. The end-use products, Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide were each of low acute toxicity by the oral, dermal and inhalation routes in rats. The products were minimally irritating to the skin and eyes of rabbits, and were not dermal sensitizers in guinea pigs according to the Buehler method.

The pharmacokinetic behaviour of ipconazole was characterized by rapid absorption and elimination from the plasma of rats. Absorption was extensive for both the low and high dose tests, but decreased at the high dose suggesting saturation of the absorption kinetics. The half-life of elimination of ipconazole was shorter in plasma than whole blood, suggesting the presence of radioactivity in the red blood cells (RBC). After repeat dosing, plasma/blood concentrations peaked 1 hour post-dosing but failed to reach steady-state. The area-under-the-curve (AUC) increased 2-fold compared to the single dose, suggesting further distribution into RBCs.

Ipconazole was extensively metabolized mainly via hydroxylation and conjugation. Unchanged parent represented approximately 2.2% of the administered dose (AD). After a single low dose of benzyl methylene-radiolabelled ipconazole, the major metabolites in urine were unidentified. Following low doses of triazole-radiolabelled ipconazole, major sex differences were observed. In male urine, only one major fraction 1,2,4-triazole (6.9% AD) was observed, whereas females had a similar urinary profile as the benzyl methylene group. All other urinary metabolites accounted for ≤1.6% of the AD. A similar metabolic profile was observed after repeat dosing; however, an increase in the polar component suggested that induction of metabolism may have occurred to a limited extent after repeat dosing. The major faecal metabolites were F22, F9, F22a and F1 in males and F9 and F10, F18, F1 and F22a in females. All other faecal metabolites accounted for less than 3.9% of the AD. The major metabolite in bile accounted for 22% of the AD and was identified as a mixture of glucuronide conjugates of M-1 and M-5. The metabolic profile in bile-cannulated rats was similar between the low and high dose groups and between sexes. Other major metabolites were identified as glucuronide conjugates. All other bile-derived metabolites each accounted for ≤3.8% of the AD.

Radioactivity was primarily observed in the liver and RBCs after administration of ipconazole, with intermediate levels observed in the kidney and thyroid gland. No differences in organ distribution were noted between radiolabels, dose levels or single vs. repeat dosing groups. There was no evidence of bioaccumulation in the tissues and expired air did not contain appreciable amounts of ipconazole.

Excretion of the low and high doses was rapid and occurred mostly via the faeces (78-82% of the AD at 48 hours). The majority of the faecal radioactivity was due to biliary excretion, suggesting significant enterohepatic circulation. Urinary excretion was virtually complete by 48 hours and accounted for 12-24% of the AD. Females in all dose groups excreted slightly more radioactivity in the urine than males, and retained slightly more in the carcass than males after high dose and repeat dose administration.

The principal target organs of ipconazole after repeat oral dosing were the non-glandular stomach in mice and rats, eyes (lens), prostate, adrenal glands and thymus in Beagle dogs and the liver across species. At higher dose levels, endocrine organs also appeared to be targeted by ipconazole, and there was evidence of possible immune system effects (increased white blood cell (WBC) parameters) in rats and dogs.

Ipconazole has irritant properties that resulted in the formation of lesions on the epithelial mucosa of the rodent forestomach. The key treatment-related effects in the forestomach starting at lower doses included: epithelial hyperplasia, hyperkeratosis, inflammation, erosion and/or ulceration. The effects observed in the non-glandular stomach of rodents are not toxicologically relevant to humans, since it is doubtful that ipconazole would be in contact with the human gastrointestinal tract for a significant length of time compared to the resident time in the non-glandular stomach of rodents. In addition, there was no evidence of treatment-related forestomach lesions in dogs, which have similar functional stomachs as humans. Consideration of such lesions influenced the dose selection for the rodent combined chronic/carcinogenicity study. The effects observed in the rat were more severe than those noted in the mouse; however, there were no significant sex differences in either species. No treatment-related non-glandular stomach lesions were observed in the combined chronic/carcinogenicity rat feeding study, as the doses administered were below the threshold which would cause excessive organ toxicity. In addition, there were no treatment-related stomach lesions in the dog or the rabbit, which have similar stomachs to humans.

Treatment-related effects in the liver after ipconazole administration consisted of increased weights, elevated liver enzyme activities and/or oil-red-O (ORO) staining (indicative of fatty change) associated with a number of microscopic findings such as: bile duct or hepatocyte proliferation, pigment laden hepatocytes or Kupffer cells, inflammation, hepatocyte vacuolation and necrosis.

Dogs appeared to be the most sensitive species to ipconazole-induced toxicity. Treatment-related ocular findings included increased incidences of anomalies of the lenticular fibres, cataracts and opacities, blepharo-oedema, and/or lenticular degeneration. Increased prostate weights were observed in the 90-day and 12-month feeding studies but lacked correlative histopathology. Increased cortical vacuolation was observed in the adrenal glands at higher doses. Decreased thymus weight and cortical atrophy were observed in males during the 28-day range-finding and 12-month studies, and females exhibited increased incidences of thymic epithelial cords and tingible body macrophages (indicative of apoptosis and/or necrosis) after 12-month administration of ipconazole. Reddening of the skin affecting single areas and leading to reddening of the entire body were observed consistently in all of the dog studies but the aetiology is unknown. Taken together with the adrenal, thymus and increased WBC effects, these findings suggest that ipconazole may cause immune stimulation or an autoimmune (lupus-like) disorder at higher doses. No immunotoxicity studies were submitted for ipconazole. The effects observed in the lens are consistent with the MOA of the triazole family of chemicals. It is well established that the plasma membrane of the lens contains a high relative content of cholesterol and that interference with the lens sterol pathway by genetic defect or chemicals can produce cataracts (Cenedella, 1996). In the range-finding toxicity studies, high doses of ipconazole were not tolerated in rats or dogs; consequently, lower high-dose levels were employed in the remainder of the short-term and long-term toxicity studies.

Dermal dosing of rats for 28 days resulted in systemic and dermal effects at 1000 mg/kg bw/day, the highest dose tested. Decreased body weight/gains associated with decreased food consumption and food efficiency were observed during the last two to three weeks of the study. Increased adrenal weight in females was associated with minimal diffuse hypertrophy and hyperplasia in the cortical region. Dermal effects included erythema during the last two weeks of the study and epidermal hyperplasia and/or skin thickening at the treatment sites.

Inhalation exposure of rats to ipconazole for 28 days caused respiratory tract irritation. A no observed adverse effect level (NOAEL) was not established in this short-term inhalation toxicity study and the lowest observed adverse effect level (LOAEL) of 30 mg/m^3 (equivalent to approximately 8 mg/kg bw/day) was based on portal of entry effects.

Ipconazole did not cause cancer in mice and rats, and was not genotoxic. However, the highest dose tested in the rat combined chronic/carcinogenicity study was not adequate based on the marginal effects on body weight gain and food efficiency in females during Week 1. The 2-generation reproductive toxicity study revealed only marginal effects on body weights and body weight gains after longer-term administration of at least 2-fold higher dose levels of ipconazole, suggesting that a longer duration of dosing at this higher level would not be likely to result in more serious systemic toxicity in rats. For this reason, the dosing was considered adequate to assess the chronic toxicity component of the study. Residual uncertainties remained for the carcinogenic potential of ipconazole in the rat.

Triazoles are frequently hepatocarcinogenic and hepatotoxic in mice treated at or near the maximum tolerated dose (MTD) while in rats, comparatively speaking, this outcome is rare under similar dosing conditions. Considering this and the absence of carcinogenic effects in mice, ipconazole is not expected to cause hepatocarcinogenic effects in rats below the dose likely to elicit forestomach lesions. In contrast, rats dosed at or below the MTD tend to exhibit greater sensitivity than mice to triazole-mediated tumourigenic and carcinogenic effects in the endocrine organs (ovaries, testes, thyroid and adrenal) and urinary bladder. Existing evidence suggests that some triazoles promote threshold carcinogenic effects by altering steroid hormone metabolism, which subsequently disrupts endocrine function (e.g. Leydig cell tumours). Ipconazole at higher doses may have comparable effects in rodents through a non-genotoxic mode of action. Sub-chronic treatment with ipconazole at doses close to the MTD resulted in increased rat adrenal and ovary weights. Mice exhibited an increased incidence of enlarged adrenals at the MTD in the carcinogenicity study. Also, ipconazole caused thyroid and adrenal gland histopathological effects in dogs, including pre-neoplastic thyroid lesions at 20 mg/kg bw/day. There was no evidence of treatment-related effects in the urinary bladder after treatment with ipconazole. While dosing was not considered adequate to fully assess the carcinogenic potential of ipconazole in the rat combined chronic/carcinogenicity study, no pre-neoplasic or neoplastic effects were evident at doses up to ~13 mg/kg bw/day.

The reproductive toxicity potential of ipconazole was assessed in a two-generation reproductive toxicity study in rats. Parental effects during the premating period included decreased body weight and/or body weight gains and reduced food consumption at $\geq$100 ppm in the first filial (F_1) generation. Similar effects occurred during gestation and/or lactation in parental and F_1 generation females at the same dose levels. Reproductive effects in 300 ppm females included increased ovary weight, prolonged regular oestrus cycles, decreased implantation sites and decreased total offspring number. Offspring toxicity was characterized by decreased body weight and/or body weight gain in F_1 and second filial (F_2) generation pups at $\geq$100 ppm. Delayed vaginal opening in 300 ppm F_1 generation females may be secondary to decreased body weight, but may also be indicative of a developmental effect. Anogenital distance was unaffected in the F_2 generation in this study. There was no evidence of increased susceptibility of the young.

Developmental toxicity was assessed in rats and rabbits. In the range-finding rat developmental toxicity study, decreased maternal body weight and body weight gains were associated with decreased foetal weights at 50 mg/kg bw/day, with clinical signs, body weight loss, decreased food consumption and mortality at higher doses. Treatment-related effects at 100 mg/kg bw/day consisted of increased placental weights and increased incidences of foetal malformations, such as microphthalmia, and kinky and/or short tails. Increased foetal resorptions and deaths (macerated foetuses or placental remnants) were observed at $\geq$50 mg/kg bw/day compared to controls. In the developmental toxicity study in rats, decreased maternal body weight gains and food consumption at 30 mg/kg bw/day were associated with decreased foetal weights and increased incidences of visceral or skeletal variations including dilatation of the renal pelvis and/or ureter, left umbilical artery and lumbar ribs.

In the rabbit developmental toxicity study, decreased maternal body weight gains or body weight loss and decreased food consumption were observed during dosing at 50 mg/kg bw/day and were associated with decreased placental weights at necropsy. Treatment-related increases in major malformations, primarily consisting of splitting of the parietal bone, were observed at maternally toxic doses. Further malformations such as short, kinky or vestigial tails, acephaly, microphthalmia and general oedema were observed at higher doses in a separate range-finding study.

There was no evidence of neurotoxicity in the acute oral rat study, in the functional observation battery (FOB) performed on 10 animals/sex/dose in the 13-week and 104-week combined chronic/carcinogenicity study in rats, or in any of the other repeat dosing studies in other species.

Overall, ipconazole was not carcinogenic or genotoxic. However, there was some concern regarding dose adequacy in the rat combined chronic/carcinogenicity study and additional toxicological data are required. There was variability in toxicological response among test species, which may reflect differences in metabolism. There were no apparent sex differences in ipconazole toxicity between male and female rats and dogs, while male mice were slightly more sensitive to ipconazole toxicity than females. Durational effects of dosing were not observed in rats, however, slight effects were observed in mice and dogs (i.e., more serious effects after a longer duration of treatment).

Results of the acute and chronic tests conducted on laboratory animals with ipconazole and its associated end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 2, 3 and 4.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes and schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, extensive data were available for ipconazole including developmental toxicity studies in rats and rabbits, and a 2-generation rat reproductive toxicity study. Throughout the database, the main target of toxicity for all species evaluated was the liver while endocrine organs were targeted at higher dose levels. While endocrine activity can be a trigger for a developmental neurotoxicity (DNT) study, no study was available for ipconazole. The endocrine effects observed in the repeat dose studies with ipconazole occur at doses above those that are used for risk assessment. In light of this information and based on the absence of neurotoxicity in adult animals, a DNT study is not required for ipconazole at the present time. However, further information, including a DNT study, may be required if aberrations in thyroid, adrenal or sex hormone levels are observed in the required data.

In the rat developmental toxicity study, decreased foetal weights and increased incidences of foetal variations, such as dilatation of renal pelvis and/or ureter, left umbilical artery and/or lumbar ribs were observed in the presence of maternal toxicity (decreased body weight/gain and food consumption during a limited period of time during dosing, increased placental weights). In the rabbit, a major malformation (splitting of the parietal bone) was observed at maternally toxic doses. Further malformations, such as microphthalmia, acephaly, general oedema and/or short, kinky, or vestigial tails and foetal resorptions and/or deaths, were observed at much higher doses in both species. There was no indication of increased susceptibility of the offspring compared to parental animals in the multi-generation reproductive toxicity study.

A degree of concern analysis was conducted as part of the consideration on the magnitude of the PCPA factor. Residual uncertainties with respect to the completeness of the data included inadequacy of dosing in the rat carcinogenicity study, which has been addressed by an additional uncertainty factor for database deficiencies, and the lack of a DNT study. As discussed above, the concern for the lack of a DNT study was offset by absence of neurotoxicity in adult animals and margin from the selected reference doses to the high-dose effects observed in endocrine organs. Qualitative susceptibility of the young was observed in the rabbit developmental toxicity study based on seriousness of the endpoint. While splitting of the parietal bone is considered a serious congenital malformation, the degree of concern is tempered by the accompanying maternal toxicity. It is recognized that maternal toxicity could, in and of itself, bring about adverse consequences in the young. In addition, these endpoints were addressed in well-conducted studies and definitive NOAELs were established, resulting in a lower overall degree of concern.

3.2 Determination of Acute Reference Dose

Females aged 13-49

The recommended acute reference dose (ARfD) for females aged 13-49 is 0.033 mg/kg bw, based on the NOAEL of 10 mg/kg bw/day in the rabbit developmental toxicity study. The findings at the LOAEL of 50 mg/kg bw/day included decreased body weight gains or body weight loss during dosing, decreased food consumption and decreased placental weights in maternal animals. These findings were associated with decreased foetal weights and increased major malformations, primarily consisting of splitting of the parietal bone. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. For the reasons outlined in the PCPA Hazard Characterization Section, the PCPA factor was retained but reduced from 10-fold to 3-fold, resulting in a composite assessment factor (CAF) of 300-fold.

The ARfD for females aged 13-49 is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw}}{300} = 0.033 \text{ mg/kg bw of ipconazole}$$

General population (excluding females aged 13-49)

An ARfD for ipconazole was not determined for the general population (excluding females aged 13-49, but including infants and children) because an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies for this population of interest.

3.3 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for ipconazole is 0.0067 mg/kg bw/day, based on the NOAEL of 2 mg/kg bw/day from three co-critical studies (12-month dog study, 18-month mouse study, 2-generation reproductive toxicity study). In the 12-month dog study, treatment-related effects at the LOAEL of 5 mg/kg bw/day consisted of increased reddening of the skin in both sexes and decreased body weight gains in females. In the multi-generation reproductive toxicity study, effects at the LOAEL of ~8 mg/kg bw/day included decreased body weight, body weight gain and food consumption in parents and offspring. In the 18-month mouse study, there was evidence of increased liver and stomach histopathology at the LOAEL of 24.1/26.0 mg/kg bw/day M/F. Collectively, these co-critical studies represent the lowest NOAELs in the database and the NOAEL of 2 mg/kg bw/day is protective of effects to the liver, lens (eyes), endocrine organs and immune system. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor for database deficiency was applied based on the inadequacy of dosing in the rat combined chronic/carcinogenicity study. The NOAEL in repeat dose studies selected for the ADI are considered protective of the effects observed in the rabbit developmental toxicity study. For this reason, it was considered appropriate to reduce the PCPA factor to 1-fold. Therefore, the composite assessment factor is 300-fold.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2\text{ mg/kg bw/day}}{300} = 0.0067\text{ mg/kg bw/day of ipconazole}$$

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

For the short-term dermal route of exposure, the NOAEL of 10 mg/kg bw/day in the rabbit developmental toxicity study, based on decreased foetal weights and increased incidences of major malformations, including splitting of the parietal bone at the LOAEL of 50 mg/kg bw/day, was considered to be the most relevant endpoint for short-term occupational and bystander dermal risk assessment. Although a 28-day dermal toxicity study in rats had a NOAEL of 150 mg/kg bw/day, this does not protect against the teratogenic concern observed in the rabbit developmental toxicity study. The worker population could include pregnant and lactating women and therefore it is appropriate to ensure adequate protection to the foetus or the nursing infant, who may be exposed via their mother. In light of concerns regarding pre- and post-natal toxicity (as outlined in Section 3.2), an additional factor of 3-fold, in addition to the standard factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, was applied. Therefore, the target margin of exposure (MOE) is 300.

For the intermediate-term dermal route of exposure, the NOAEL of 10 mg/kg bw/day in the rabbit developmental toxicity study, based on decreased foetal weights and increased incidences of major malformations, including splitting of the parietal bone, was considered to be the most relevant endpoint for intermediate-term occupational and bystander dermal risk assessment. Although other repeat dosing studies of an appropriate duration resulted in lower NOAELs than the selected endpoint, the forestomach and liver effects in the 90-day rodent feeding studies would have been detected in the 28-day dermal toxicity study, and are not of toxicological concern for this scenario. The overall NOAEL for eye effects in dogs is 5 mg/kg bw/day, however, application of the standard uncertainty factors (i.e., 100-fold) to this NOAEL would not protect against the teratogenic concern in the rabbit developmental toxicity study. Therefore, the rabbit was chosen as the most relevant species for intermediate-term dermal scenarios. The target MOE is 300 for the reasons outlined above in the short-term dermal section.

For the short-term and intermediate-term inhalation route of exposure, the LOAEL of 8 mg/kg bw/day from 28-day rat inhalation toxicity study, based on treatment-related portal of entry irritation, was considered to be the most relevant endpoint for occupational and bystander inhalation risk assessment. The target MOE of 300 includes a 10-fold uncertainty factor for interspecies extrapolation, a 10-fold uncertainty factor for intraspecies variability and an additional 3-fold uncertainty factor for extrapolation from a LOAEL to a NOAEL. This endpoint is protective of the effects observed in the rat and rabbit developmental toxicity studies and provides a margin of 375 to the developmental NOAEL of 10 mg/kg bw/day. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

No dermal absorption data were available for ipconazole, the active ingredient in these products, as such, a default dermal absorption value of 100% was used in the dermal risk assessment.

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide during mixing, loading and treating seed, contacting contaminated seed treatment equipment and handling and planting treated seed.

Commercial Seed Treatment
Exposure to workers treating corn seed with Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide is expected to be of short- to intermediate- term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for workers treating corn seed with Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide using commercial seed treatment equipment. The exposure estimates are based on treaters and baggers wearing long pants, long-sleeved shirts and chemical resistant gloves.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Since the proposed label states that Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide are intended for use by commercial seed treatment applicators only, on-farm seed treatment was not considered in the risk assessment.

For Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide applied to corn seed, dermal and inhalation exposure estimates for workers treating and bagging were generated from a surrogate exposure study measuring exposure to workers treating and bagging canola seed treated with isofenphos.

The surrogate study was conducted to quantify inhalation and dermal exposure of workers during commercial seed treatment of canola seed with Oftanol (technical isofenphos) and Benlate T at an application rate of 12 g-isofenphos/kg seed. Monitoring was done for isofenphos only. Workers monitored in this study included a mixer/loader, a coater, a bagger, and a shift foreman. The study was conducted in Alberta. Four workers were monitored 3 times for a total of 12 replicates. The maximum amount of active ingredient handled per replicate was 92 kg. The average duration of each replicate was 7.4 hours.

Dermal exposure was estimated using passive dosimetry. Deposition was measured using dermal patches attached to the inner and outer clothing of each worker. Deposition to the hands was measured using ethanol hand washes. Total dermal exposure was calculated by extrapolating the patch data to standard body surface areas, and summing all body area results together with the handwash residues. Inhalation exposure was measured using air filters attached to personal air sampling pumps.

The total dermal exposure (patch deposition and hands) was added to the inhalation results for each worker, and normalized for kg a.i. handled. The mean total exposure was highest for mixer/loader (189.28 µg/kg-a.i.), followed by shift foreman (98.02 µg/kg-a.i.), coater (33.29 µg/kg-a.i.) and bagger (20.54 µg/kg-a.i.).

These estimates are based on a closed mix/loading system with workers wearing long pants, long-sleeved shirts and chemical resistant gloves. Estimates are based on workers with no head covering, and no respirators.

The major limitation of this study was that only 4 workers at one test site were monitored. A greater sample size with additional plants would have allowed for a more accurate comparison between individuals and between plants.

Dermal exposure was estimated by coupling the unit exposure values from the surrogate study with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 300.

Studies using canola seed treatment have previously been used as surrogates to represent exposure to workers treating corn seed; however, corn seed is expected to be dustier than canola seed. As such, bridging data are required to demonstrate the applicability of using exposure data to workers treating canola to estimate exposure to workers treating corn.

Margins of exposure for all seed treatment workers treating corn with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide are above the target MOE for both dermal and inhalation exposure (Appendix I, Table 5). The personal protective equipment (PPE) for workers in the study is the same as that on the Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide labels. Since a closed mix/load system was used in the surrogate study, closed mixing/loading was required on the Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide labels.

Since the MOEs are significantly higher than the target MOE of 300 for both dermal and inhalation exposure, the surrogate study on canola used in the risk assessment to estimate exposure to corn is considered acceptable on a conditional basis, pending suitable additional supporting data or rationale.

Exposure to workers treating wheat, barley, oat, rye and triticale seed with Rancona Apex Fungicide is expected to be of short- to intermediate- term in duration and to occur primarily by the dermal and inhalation routes. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Since the label states that Rancona Apex Fungicide is intended for use by commercial and on-farm seed treatment applicators, both of these scenarios were considered in the risk assessment.

Dermal and inhalation exposure estimates for commercial workers treating and bagging cereal seed with Rancona Apex Fungicide were generated from a surrogate exposure study measuring exposure to workers treating and bagging wheat seed treated with BAYTAN 312 FS containing the active ingredient Triadimenol (Dean, 1993). The study was conducted at three different facilities in Ontario, Canada to estimate and compare exposures at large, medium, and small size treatment facilities. Workers were monitored for half-day replicates over 2 or 3 days at each facility for a total of 55 half-day replicates. The maximum amount of active ingredient handled per replicate was 21.9 kg. The average duration of each replicate was approximately 3.0–3.5 hours.

Dermal exposure was estimated using dermal patches attached to the inner and outer clothing of each worker. Deposition to the hands and gloves was measured using ethanol handwashes. Total dermal exposure was calculated by extrapolating the patch data to standard body surface areas, and summing all body area results together with the handwash residues. Inhalation exposure was measured using air filters attached to personal air sampling pumps. All results were corrected for field recovery, where necessary. The study was conducted according to current guidelines, and no major limitations were identified.

Each worker was monitored for half of a work day and wore their normal work clothing, consisting of long pants, long-sleeved shirts and chemical resistant gloves. The total dermal exposure (patch deposition and hands) was added to the inhalation results for each replicate, and normalized for kg a.i. handled. The arithmetic mean value was calculated for each job at each site. A summary of the results is shown in Appendix I, Table 6.

These results are based on half-day replicates for workers wearing long-sleeved shirts, long pants and chemical resistant gloves.

The mixer/calibrator at each facility prepared the treatment mixture by weighing each component by hand, and placing it into a 200 L drum. The mixture consisted of approximately 6 kg of seed colourant, 43 kg Baytan, and 156 kg water. The drum served as a temporary mix tank which the worker rolled back and forth to mix the components. The drum was then attached to the treatment equipment. During disassembly, the worker was monitored disconnecting the hoses and fittings from the drum containing the treatment mixture, cleaning the drum and loading it into a transport van. The study authors stated that these activities and equipment were not typical for most treatment plants, and are not considered relevant for exposure assessment. As such, the mixer/calibrator was excluded when estimating exposure for workers in a commercial seed treatment facility.

The highest mean dermal and inhalation unit exposure values, excluding the mixer/calibrator for medium facilities (689.73 µg/kg a.i handled and 245.74 µg/kg a.i. handled for dermal and inhalation exposures, respectively) were used to estimate exposure to workers treating small cereal grains with Rancona Apex Fungicide.

Margins of exposure for dermal and inhalation exposure for workers treating small cereal grain seed with Rancona Apex Fungicide at commercial seed treatment facilities are above the target of 300 (Appendix I, Table 7) for workers wearing a single layer plus chemical resistant gloves. These estimates are expected to overestimate exposure for most commercial seed treatment workers since a dermal penetration value of 100% was used in the risk assessment.

Since oats are expected to have a higher dust off potential than wheat, which was used in the surrogate commercial treating study, and the estimated MOEs are relatively close to the target, the registration of Rancona Apex Fungicide can be conditionally supported on oats pending a suitable bridging rationale or a dust off study comparing the dust off potential of wheat with that of oats.

On-farm Seed Treatment and Planting

Exposure to farmers treating small cereal grain seed on-farm and planting treated seed is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure. Chemical-specific data measuring exposure to workers treating cereal grains on-farm were not submitted. Dermal and inhalation exposure estimates for farmers treating small grain seeds on-farm with Rancona Apex Fungicide and planting treated seed were generated from a surrogate study measuring exposure to workers treating wheat and barley seed on-farm with Vitaflo 280 Fungicide and planting treated seed.

The target application rate in the study was 330 mL product/100 kg of seed (57 g a.i./100 kg seed). The maximum proposed application rate of Rancona Apex Fungicide on small grain cereals was 2 g a.i./100 kg seed. The application rate used in this exposure study was higher than that proposed for Rancona Apex Fungicide. The type and amount of seed treated, the treatment equipment and study location are representative of the proposed use pattern; however, the protective equipment used in the study was more protective that the PPE specified on the proposed product label.

Sixteen workers were monitored using inner dosimeters, face/neck wipes and handwash samples to estimate dermal exposure and air sampling tubes to estimate inhalation exposure. The inner dosimeters were worn under a long-sleeved shirt and long pants, additional protective equipment worn included cloth coveralls, a dust mask, goggles, chemical resistant gloves and shoes plus socks. Planting was done with closed cab tractors. Workers handled an average of 4.24 kg a.i. (range 1.74- 6.94 kg a.i.) and planted an average of 54.3 ha (range 26.4- 86.0 ha) of treated seed. The average monitoring period was 9.2 hours and ranged from 6.2 to 13.4 hours.

Overall, the study was well conducted and the data quality is adequate for risk assessment purposes. The mean dermal exposure, when adjusted for the amount of active ingredient handled, was 111.84 g/kg a.i. handled. The hands constituted the majority (approximately 58%) of dermal exposure. Of the residues measured on inner dosimeter sections, the majority was on lower arm sections. The mean inhalation exposure when adjusted for the amount of active ingredient handled was 20.6 g/kg a.i. handled.

Field recovery for air sampling tubes at the low fortification level was low (45.3%). Nine of the sixteen inhalation residue values were corrected for this low field recovery. As well, the air sampling tubes were stored for up to 469 days prior to analysis. Two samples were stored for slightly longer than the field fortified samples. These limitations reduce the confidence in the inhalation unit exposure value. However, since inhalation exposure is not the principal route of exposure in this study, this study limitation is not expected to have a serious effect on the data.

Margins of exposures for workers treating and planting wheat and barley grain seed with Rancona Apex Fungicide on-farm are above the target of 300. However, since the protective clothing worn by the workers in the study was higher than that proposed on the Rancona Apex Fungicide label, and it was not possible to extrapolate to other clothing scenarios, coveralls over a single layer of clothing and closed cab tractors were required during on-farm treatment and planting on the product label for Rancona Apex Fungicide.

Oats are expected to have a higher dust off potential than wheat and barley, which were used in the surrogate on-farm treating and planting study. Since the MOEs for workers treating seed on-farm and planting are significantly higher than the target MOE of 300 for both dermal and inhalation exposure, the registration of on-farm treatment with Rancona Apex Fungicide on oats were supported on a conditional basis pending suitable additional supporting data or bridging rationale. A study comparing the dust off potential of wheat treated with Vitaflo 280 Fungicide with that of oats treated with Rancona Apex Fungicide may be sufficient as bridging data. However, if the dust off study demonstrates a much higher dust off potential for oats treated with Rancona Apex Fungicide than for wheat treated with Vitaflo 280 Fungicide, further exposure data may be required.

3.4.2.2 Exposure and Risk Assessment for Workers Handling Treated Seed

Workers planting corn seed treated commercially with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide have the potential to be exposed to ipconazole. Exposure is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure.

No chemical specific data were submitted by the registrant to represent exposure to workers planting corn seed treated commercially with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide. Dermal and inhalation exposure estimates for workers planting treated seed were generated from a surrogate exposure study measuring exposure to workers planting canola seed treated with isofenphos.

This post-application passive dosimetry study monitored four private growers, each serving as a subject three or four times, for a total of thirteen replicates during loading and planting of canola seed treated with a mixture containing Oftanol (technical isofenphos) and Benlate T. Monitoring and sample analysis was for isofenphos and its oxygen analog. The study was conducted in Manitoba. Work involved loading the treated seed (25 kg bag) into seed hoppers and planting between 6.7 - 9.0 kg seed/ha using tractor driven planters. The duration of each replicate was between 1.83 hrs - 6.24 hrs and each worker handled between 0.86 - 2.81 kg a.i./replicate.

Dermal deposition was measured using patches attached to the inner and outer clothing of each worker. Deposition to the hands was measured using ethanol handwashes. Potential inhalation exposure was measured using air filters attached to personal air sampling pumps.

Total exposure was estimated for workers wearing a typical clothing scenario for seed planting including long-sleeved shirt and long pants and wearing chemical resistant gloves while handling the treated seed. Total dermal exposure was calculated by extrapolating each interior patch data and two exterior patches (upper back and head) to standard body surface areas, and summing results for total body deposition and adding the handwash residues. Inhalation exposure was calculated based on the amount of isofenphos found on the air-sampling filters, the pump flow rate, and an assumed respiratory rate of 29 L/minute (0.029 m^3/minute) for moderate activities. Since workers were not monitored for a full work day, results were normalized to µg/kg-a.i. handled. Based on the typical clothing scenario, the mean total exposure (body + hands + inhalation) was 425.28 245.79 µg/kg-a.i. handled and ranged from 183.55 to 947.02 µg/kg-a.i. handled.

The major limitation of this study was that only 4 workers were monitored. A greater sample size would have allowed for a more accurate comparison between individuals. Other minor limitations did not affect the outcome of the study.

Dermal exposure was estimated by coupling the unit exposure values from the surrogate study with the amount of product handled/day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled/day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (NOAELs) to obtain the MOE; the target MOE is 300.

Margins of exposures for workers planting corn seed treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide (Appendix I, Table 9) are above the target MOE for both dermal and inhalation exposure for workers wearing long- sleeved shirts, long pants and chemical resistant gloves while handling the treated seed. As for commercial workers, since the MOEs are significantly higher than the target MOE of 300 for both dermal and inhalation exposure, the surrogate study on canola used in the risk assessment to estimate exposure to corn is considered acceptable on a conditional basis, pending suitable additional supporting data or rationale.

Workers planting cereal grain seeds treated with Rancona Apex Fungicide also have the potential to be exposed to ipconazole. Exposure is expected to be of short- to intermediate-term in duration and to occur via the dermal and inhalation routes of exposure.

Since MOEs for workers treating and planting wheat and barley grain seed on-farm are above the target of 300 (Appendix I, Table 8), exposure for workers planting wheat, barley, oat, rye and triticale treated commercially with Rancona Apex Fungicide is expected to be above the target as well.

3.4.3 Residential Exposure and Risk Assessment

There are no domestic class products; therefore, a residential handler assessment was not required.

3.4.3.3 Bystander Exposure and Risk

For application at commercial seed treatment facilities where the products and seeds are handled indoors, bystander exposure should be negligible. For on-farm application and planting of treated seeds, drift and bystander exposure is expected to be minimal.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products and animal commodities is ipconazole. The residue definition for risk assessment in plant products is ipconazole, 1,2,4-T and the conjugated triazole metabolites (e.g., TA, TAA and TP) and in animals is ipconazole and 1,2,4-T. The data gathering and enforcement analytical methodologies are valid for the analytes of interest in plant commodities. The residues of ipconazole are stable, when stored in a freezer at -20°C for up to 13 months.

Residue data from trials conducted in the NAFTA representative growing regions using the end-use product containing ipconazole on corn, wheat and barley are sufficient to support the establishment of a maximum residue limit for Crop Group 15 (except rice). Residue data from trials conducted in NAFTA representative growing regions in or on peanuts, soybeans, and crop subgroup 6C (except soybeans) are sufficient to establish import maximum residue limits. Raw agricultural commodities were not processed due to the lack of quantifiable residues.

No quantifiable residues of ipconazole are anticipated in rotational crops or in livestock matrices.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.03). The free triazole (1,2,4-T) and conjugated triazole metabolites, which are common to many other triazole herbicides, are part of the residue definition for risk assessment. However, due to the prevalence of these metabolites in the environment and evidence of different toxicological properties, separate aggregate risk assessments must be conducted for the free triazole and conjugated triazole metabolites. The United States Environmental Protection Agency recently updated the human health aggregate risk assessment for triazole-derivative fungicide compounds to include the proposed uses for ipconazole (http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=09000064807860a4). At this time, PMRA is investigating a path forward to address the aggregate human health exposure to these triazole metabolites.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

A basic chronic dietary exposure assessment was performed taking into account proposed MRLs. Aggregate exposure to ipconazole from food and water is considered acceptable: 0.4% to 1.7% (0.000028 to 0.000114 mg/kg bw/day) of the ADI for the total population. The highest aggregate exposure and risk estimate is for children 3-5 years old at 1.7% (0.00114 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

A basic acute dietary exposure assessment was performed taking into account proposed MRLs for crops matrices. Aggregate exposure from food and water is considered acceptable: 0.25% (0.000084 mg/kg/day) of the ARfD for females 13–49 years old.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for ipconazole consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Crop Group 15: Cereal Grains (except rice)	0.01
Peanuts	0.01
Soybeans	0.01
Crop Subgroup 6C: Dried shelled pea and bean (except soybean)	0.01

For additional information on MRLs in terms of the international situation and trade implications, refer to Appendix II. For the list of crops included in the specified crops groups, refer to Appendix III.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 10, 11 and 12.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Ipconazole can enter the environment through dislodging from treated seed surfaces during and after seeding. Based on laboratory studies, ipconazole adsorbs strongly to various soil types (adsorption coefficient (K_{oc}) ranged from 2029 - 3492). The mobility of ipconazole is classified as low to immobile.

Ipconazole is persistent in the terrestrial environment with biotransformation in soil being the principal route of dissipation (half-life values ranging from 180 to 750 days for aerobic conditions, and 779 days under anaerobic conditions). A proposed transformation pathway in soil systems, based on laboratory studies conducted on United Kingdom soils under aerobic and anerobic conditions, indicates that ipconazole proceeded via KNF-317-M-1 and KNF-317-M-11 transformation products to form CO_2 and bound residues. 1,2,4-Triazole is also present in the transformation pathway, likely before the formation of CO_2 and bound residues. The triazole is the only major transformation product determined from laboratory studies; however, this transformation product ultimately dissipates to relatively low concentrations in the environment. Although no Canadian terrestrial field dissipation study was submitted, ipconazole is likely to carry over in soil to the following growing season based on transformation data from laboratory studies [time to 90% dissipation (DT_{90}) ranging from 600 to 1100 days at 20 to 25°C, and up to 2000 days at 10°C].

Under the proposed use pattern, concentrations of ipconazole in surface waters are expected to be minimal as this chemical is not significantly susceptible to leaching or runoff. Ipconazole scored a low value under the Gustafson model, and is classified as a non-leacher to borderline leacher. Water modeling indicated that only low levels of ipconazole would be detectable in groundwater (0.0098 µg a.i./L, for daily and yearly averages) and surface water (0.12 to 0.28 µg a.i./L for daily averages, and 0.029 to 0.26 µg a.i./L for yearly averages) sources of drinking water. Ecoscenario modeling (taking into account crop type, timing of application, and water depth) also indicated that surface runoff of ipconazole would result in low estimated environmental concentrations (EECs) (0.056 to 0.14 µg a.i./L in surface waters). Therefore, based on an assessment using known criteria and modeling results, leaching or runoff of ipconazole into surface waters is expected to be minimal.

Ipconazole will, however, be persistent if it enters surface waters, as was shown by results of water and ecoscenario modeling. In laboratory studies, ipconazole did not dissociate at any pH tested, and aqueous photolysis was not considered to be a significant route of transformation.

The aerobic aquatic biotransformation was not characterised, as no data were submitted; the parent compound is, however, assumed to be stable under aerobic aquatic biotransformation conditions. An anaerobic aquatic biotransformation study was also not submitted; however, the results of an anaerobic aquatic soil study indicated that ipconazole is expected to be similarly persistent under anaerobic aquatic conditions.

Ipconazole is not expected to be bioaccumulative in terrestrial and aquatic organisms, based on results from mammalian and fish studies (Appendix I, Table 15).

For a summary of the environmental fate of ipconazole and a list of transformation products, see Appendix I, Tables 13 and 14.

4.2 Environmental risk characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with effects concentrations. Estimated environmental exposure concentrations are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risk to Terrestrial Organisms

The assessment of risk of ipconazole to terrestrial organisms was based upon the evaluation of five bird studies (acute gavage, dietary exposure, reproduction) and four mammalian studies (acute gavage, two generation reproduction, development). No studies related to toxicity of ipconazole towards terrestrial invertebrates or plants were submitted. The requirement for these latter studies was assessed by the PMRA, and it was determined that these studies are not necessary because minimal exposure is expected to these organisms based on the current use pattern (seed treatment).

4.2.1.1 Terrestrial Vertebrates

Birds and mammals were identified as the terrestrial organisms most likely to be exposed from the use of ipconazole as a seed treatment, as they may consume treated seeds. The acute oral LD_{50} of ipconazole for bobwhite quail was 96.2 mg a.i./kg bw. Dietary effects of ipconazole also occurred with bobwhite quail, where some mortality was observed at mid to higher doses over the test range of the study. No mortality was observed with the mallard duck through dietary exposure; however, body weight gains were reduced only at the mid-dose treatment level of the study. Reproductive effects were observed for bobwhite quail for survivors/number of hatchlings, survivors/number of eggs set, hatchling survival/pen, and survivors/number of live embryos. No reproductive effects of ipconazole towards mallard test species were observed up to the highest dose tested. Acute oral, reproductive, and developmental effects were observed in laboratory studies with small mammals. Acute LD_{50} values were 888 mg a.i./kg bw and 468 mg a.i./kg bw for female rat and mouse, respectively. Parental body weight and reproductive parameters for the rat were affected by ipconazole, as was offspring body weight. Effects on maternal body weight and fetal weight were observed for the rat in the developmental study, with a NOAEL of 10 mg a.i. kg bw/day. There was no evidence of teratogenic effects due to ipconazole. There was no evidence of bioaccumulation in the tissues. The ipconazole parent compound was extensively metabolized mainly via hydroxylation and conjugation.

A screening level risk assessment was conducted for birds and mammals using the most sensitive endpoints generated from the studies that were submitted, and assuming a diet of 100% contaminated seeds. The most sensitive endpoints used were the calculated lethal dose that causes 50% mortality (LD_{50}) for acute oral gavage and dietary studies, and the no-observable-effects-limit (NOEL) for the reproductive studies. For this screening level assessment, the dietary and reproductive concentration endpoints for birds (LC_{50} and NOEC, respectively) were converted to a daily dose (LD_{50} and NOEL). This is calculated based on reported average food ingestion rates (FIR) and body weights (bw) for the exposure period of the toxicity test using the following equation.

Daily dose (LD_{50} or NOEL, mg a.i./kg bw/day) = Concentration in food (LC_{50} or NOEC, mg a.i./kg diet) × FIR (kg diet/day) / bw (kg bw)

Additionally, for the bird and mammal screening level assessment the acute toxicity endpoint (LD_{50}) is divided by an uncertainty factor of 10 to account for potential differences in inter- and intra- species sensitivity as well as varying protection levels (e.g, community, population, individual). The chronic endpoint (i.e., NOEL) is used without an uncertainty factor. Risk quotients (RQ = exposure/toxicity) are compared to a LOC of 1 for birds and mammals.

The general method for conducting the assessment is to, first, determine the amount of ipconazole present on individual seeds based on the label application rate, and then to determine the amount of treated seeds required to be consumed to equal the appropriate toxicity endpoint (as a daily dose). Next, the number of seeds that are expected to be consumed by a generic-sized group of birds and mammals is calculated (using FIR of 5.1, 19.9, and 58.1 g diet/day, for 20, 100, and 1000 g birds, respectively, and 2.2, 4.5, and 68.7 g diet/day, for 15, 35, and 1000 g mammals, respectively). These values (representing the potential exposure) are then divided by the respective values for the amount of seeds required to be consumed (equal to the toxicity endpoints; i.e., LD_{50} divided by 10, or NOEL) to calculate the RQs.

The calculated RQs for birds and mammals when consuming a corn diet indicated that the LOC was exceeded for small and medium sized birds based on reproductive effects, and for small and medium sized mammals for parental and offspring effects. The calculated RQs for birds and mammals, when consuming a wheat diet, indicated that the LOC was exceeded for small sized mammals for parental and offspring effects. As a result, a refined assessment was conducted for birds and mammals for these exposure scenarios.

The risk to birds and mammals that eat treated seeds, observed at the screening level assessment, assumes that 100% of the seeds are available for consumption. Realistically, only a small fraction of the applied treated seeds would likely be available for consumption to birds and mammals due to incorporation of seeds into the soil. In addition, some of the active ingredient from the seed surface may be dislodged during the seeding. With less treated seeds and active ingredient consumed, the RQ values would be less than presented in the screening level assessment. However, in a worst case scenario where a particular animal does consume 100% available treated seeds daily, the lowest observed effects levels (LOELs) determined for the laboratory studies would not be reached, based on RQ values not exceeding the level of concern for either corn or wheat. Therefore, the use of ipconazole as a seed treatment poses negligible risk to birds and mammals. Mitigating label statements, recommending burial of treated seed and cleanup of spilled treated seed, were required.

For a summary of the toxicity of ipconazole to terrestrial organisms see Appendix I, Table 15. For a summary of the screening level risk assessment on birds and mammals see Appendix I, Table 16 for corn seed and Table 17 for wheat seed. For a summary of the refined risk assessment on birds and mammals see Appendix I, Table 18 for corn seed and Table 19 for wheat seed.

4.2.2 Risk to Aquatic Organisms

The assessment of risk of ipconazole to aquatic organisms was based upon the evaluation of two freshwater invertebrate studies (acute, chronic), and three fish studies (two acute species, early life stage). No studies related to toxicity of ipconazole towards marine invertebrates, marine vertebrates, or marine or freshwater plants were submitted. The need for these latter studies was assessed by the PMRA, and it was determined that these studies are not required because minimal exposure is expected to these organisms based on the current use pattern (seed treatment).

4.2.2.1 Freshwater aquatic invertebrates

Two studies were submitted to assess the acute and chronic effects of ipconazole on *Daphnia magna*. In a 46 hour exposure, the LC_{50} was 1.7 mg a.i./L. In a 21-day chronic exposure, there was a sublethal effect of a reduction in the length of the surviving adults (NOEC = 0.0109 mg/L). Additionally, production of offspring in the treated groups indicated that ipconazole had an effect on the fecundity of daphnids and on the time to first brood. The most sensitive endpoint was the growth (length) of daphnids.

Using endpoint values of the lethal concentration to cause 50% mortality (LC_{50}, for the acute study) divided by an uncertainty factor of 2 (uncertainty value of 2 is used, in the case of invertebrates, to account for potential differences in species sensitivity as well as varying protection levels), and the no-observable-effects -concentration (NOEC, the endpoint value used for the chronic study), and an EEC in a water depth of 80 cm (depth used for screening level assessment of pelagic invertebrates), risk quotients calculated for the screening level did not exceed the level of concern for acute and chronic exposures. Ipconazole is not expected to pose a risk to *Daphnia* and, therefore, is not expected to pose a risk to aquatic invertebrates.

4.2.2.2 Freshwater aquatic vertebrates

Two acute studies and one early life-stage study for fish were submitted. The two acute studies were conducted over a 96 hour exposure with the bluegill sunfish and the rainbow trout. Mortality was observed for both fish species (LC_{50} = 1.3 and 1.5 mg a.i./L, respectively). Using the acute endpoint value (LC_{50}) divided by an uncertainty factor of 10 (uncertainty value of 10 is used, in the case of fish, to account for potential differences in species sensitivity as well as varying protection levels), and using the EEC value for an 80 cm water depth (depth used for screening level assessment for fish), RQ values for acute exposure did not exceed the level of concern.

The early life-stage exposure study was conducted over 28 days with the fathead minnow, and ipconazole affected post-hatch fry survival, and fry growth (NOEC = 0.00018 mg/L). Using the NOEC value in the risk quotient, the RQ exceeded the level of concern. Therefore, a tier I risk assessment was conducted for an early life-stage fish exposure.

No studies were submitted addressing the potential toxicity of ipconazole to amphibians. In *lieu* of an amphibian study, the acute (LC_{50}) and early life-stage (NOEC) endpoints for the most sensitive fish species are used as surrogates in the RQ calculation. Using the EEC value in a 15 cm water depth (depth used for screening level assessment of amphibians), the RQ value exceeds the level of concern for the chronic exposure only. Therefore, a tier I risk assessment was conducted for a chronic amphibian exposure.

As risk was observed during the screening level assessment for the chronic fish and amphibian endpoints (RQ values > 1.0), a tier I (refined) risk assessment was conducted for these organisms. The tier I assessment considers the concentrations of ipconazole in waterbodies due to runoff under several different ecoscenarios that encompass crop type, waterbody type and depth, and timing of application. For these ecoscenarios, an average expected concentration in water is determined for various time frames (i.e, over 96 hours, 21 days, 60 days, 90 days, and yearly), and for 15 and 80 cm water depths. In the case of the endpoint used in the tier I assessment, the early life-stage fish NOEC of 0.00018 mg a.i./L, the duration of the test where this value was generated was 28 days. From the ecoscenario modeling output, the surface water concentration of ipconazole representing the nearest time frame to this duration was 21 days. The average concentration of ipconazole in a 80 cm water depth (for the fish assessment), and a 15 cm water depth (for the amphibian assessment) from the ecoscenario output for corn (the highest values observed from the modeling) were 0.000059 mg a.i./L and 0.000061 mg a.i./L, respectively. The results indicate that risk associated with exposure of ipconazole to the fish early life- stage and amphibians is negligible.

For a summary of the toxicity of ipconazole to aquatic organisms see Appendix I, Table 15. For a summary of the screening level risk assessment on aquatic organisms see Appendix I, Table 20. For a summary of the Tier I aquatic risk assessment see Appendix I, Table 21.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

For Rancona Apex Fungicide, a total of 85 efficacy trials were submitted in support of the label claims: nine trials on true loose smut of barley (four of which included leaf stripe of barley); six trials on loose smut of wheat; seven trials on common and false loose smut of barley; ten trials on common bunt of wheat; seven trials on *Aspergillus*; six trials on *Penicillium*; 19 trials on seed-borne *Fusarium*; eight trials on soil-borne *Fusarium*; nine trials on seed-borne *Cochliobolus*; and four trials on soil-borne *Cochliobolus*. Field trials were conducted in Canada and the United States on wheat and barley crops. Rationales were provided to extrapolate disease claims to oats, rye and triticale. Rancona Apex Fungicide applied at the proposed rates provided control of bunt and smut diseases of wheat and barley as well as leaf stripe, seed rot diseases caused by *Aspergillus spp.* and *Penicillium* spp., and seed rot and seedling diseases caused by *Fusarium* spp. and *Cochliobolus sativus*. The proposed seed treatment with Rancona Apex Fungicide also resulted in suppression of seedling root diseases caused by *Fusarium* spp. and *C. sativus*. The performance of Rancona Apex Fungicide was comparable to the commercial standards, when an appropriate standard was used, in all trials. As a seed treatment, the impact of Rancona Apex Fungicide on pathogen resistance development is minimal, as it will only be applied once per season. Additional data have been requested in support of the claim of control of post-emergence damping-off caused by seed- and soil-borne *C. sativus*.

For Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide, data to support label claims were generated from 18 lab/greenhouse trials (bioassay and inoculated soil screen) and 12 field trials conducted in Ontario, Saskatchewan and Manitoba. Trials assessed field, sweet and popcorn seed treated at a rate of 5.6 mL product/100 kg seed (2.5 g a.i./100 kg seed). The proposed seed treatment resulted in control of *Aspergillus* spp., *Cladosporium* spp., *Rhizopus* spp., seed- and soil-borne *Fusarium* spp., and *Rhizoctonia solani* and suppression of *Penicillium* spp. Performance of Rancona 3.8 FS Fungicide / Vortex FL Seed Treatment Fungicide was comparable to the commercial standards. Tank mixes with Allegiance FL and Poncho 600FS did not result in a loss of fungicide or insecticide efficacy. No phytotoxic effects were observed as a result of the tank mixes and the products were physically compatible. Although control was observed in greenhouse trials, field trials submitted to support claims on *Fusarium* spp. exhibited very high disease pressure, which confounded plant emergence data and made it difficult to evaluate activity of the fungicide against the pest in natural conditions. In addition, no field trials were conducted on *R. solani*, although greenhouse data indicated good control. To confirm results from greenhouse data, additional field data have been requested for seed rot/pre-emergence damping-off and post-emergence damping-off caused by soil-borne *Fusarium* spp. and *R. solani*.

5.2 Phytotoxicity to Host Plants

For Rancona Apex Fungicide, treated seed lots of barley, oats, rye, triticale, and wheat were germinated on a blotter and evaluated for any negative effects on germination and growth. No negative effects on germination or plant growth were observed at the label rate or at twice the label rate. Seed stored prior to testing for 6 months, 13 months, and 18 months found that Rancona Apex Fungicide applied at label rate had similar germination to the untreated check. Rancona Apex Fungicide did not negatively affect germination, field emergence or plant growth in any germination or field trials.

Four lab studies and six field trials were reviewed to determine if seed treatment with Rancona 3.8 FS Fungicide / Vortex FL Seed Treatment Fungicide applied alone or with the proposed tank mixes caused any adverse effects. No phytotoxicity, abnormal seedlings or reduced efficacy was observed in any study.

5.3 Economics

Predictions on the net economic benefit to growers by treating seed with Rancona Apex Fungicide are influenced by the level of response of the crop, the price received for grain and the cost of Rancona Apex Fungicide. An increase in yield in response to reduced disease at the seedling stage would recover the cost of the use of Rancona Apex Fungicide and generate a profit for growers, even at low commodity prices. Rancona Apex Fungicide can also potentially increase the grade of grain by reducing the presence of a pest that lowers grain quality. Since a grade increase would apply to the total harvested crop yield, the cost of Rancona Apex Fungicide is readily recovered when the control of a pest results in a higher grade of grain. Rancona Apex Fungicide controls many important diseases of cereal crops and will be a valuable tool for growers in the production of small grain crops.

Grain corn is an important crop in Canadian agriculture. In 2006, corn was grown on more than 1.1 million hectares, which produced nearly 9 million metric tonnes of grain. Corn prices tend to be low compared to pulse and oilseed crops. Nonetheless, corn contributes more than any other crop in terms of total farm value in Ontario and is the most important field crop grown in Quebec. Canada cannot produce all of the corn it requires, so any increase in corn production lessens Canada's dependence on corn imports. Sweet corn accounted for about 3% of seeded corn acreage in 1996, and the fresh market was worth $12.5 million in 2002. The total sweet corn market in Ontario (total of fresh market sales and sales to processors) has exceeded $20 million since 2001. In terms of farm value, the Ontario sweet corn market represents about 3-4% of the farm value of commercial vegetable crops and was worth $23.2 million in 2004. In Canada, 100% of the corn seed is treated with a fungicide prior to planting. Since corn is a weak competitor early in the growing season, seed- and soil-borne diseases can impact seedling survival. Compensation in the form of cob size or grain weight can never adequately recuperate losses due to low emergence. In Ontario, the impact of seedling diseases ranges from minor to severe (replant) depending on the year and field conditions. The addition of Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide to the corn market will increase the number of pest control products a grower has to control seed and seedling diseases and will result in increased competition among products.

5.4 Sustainability

5.4.1 Survey of Alternatives

Several seed treatments are currently registered on small grain cereals. Differences exist between seed treatments as to the number of crops registered, pests controlled, use restrictions and pricing. See Appendix I, Table 22 for further information on alternatives.

Several seed treatments are available for the control of seed rot and seedling blight pathogens on corn. Ipconazole is an alternative chemistry seed treatment for corn growers to control a broad range of pathogens at the seedling stage. See Appendix I, Table 23 for further information on alternatives.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Rancona Apex Fungicide controls a broad spectrum of pests and includes uses on rye and triticale crops, which are not registered uses on some of the alternative fungicide labels. Seed treatments used in conjunction with different cultural practices can compliment and act additively to reduce disease losses.

Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide offer an alternative seed treatment option for corn to growers.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Rancona Apex Fungicide, Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide contain a Group 3 fungicide. Group 3 fungicides are demethylation inhibitors (DMI), which exhibit medium risk of pest resistance development. Recommendations from the Fungicide Resistance Action Committee include tank-mixing and alternation of pesticides with different modes of action, as well as following use directions and rates and implementing integrated pest management practices to reduce the need for fungicides. As a seed treatment, crops receive a single application of ipconazole, which acts systemically to protect the crop throughout a potential disease epidemic. Currently, there are several Group 3 seed treatment products available for cereal crops. A spray program must take the seed treatment into consideration to avoid consecutive applications of Group 3 fungicides on high-risk pathogens. Annual rotation of seed treatments with a different mode of action is also recommended.

5.4.4 Contribution to Risk Reduction and Sustainability

Application of ipconazole as a seed treatment contributes to risk reduction in several ways. Use of seed treatments delivers a low dosage of active ingredient on a per hectare basis. The delivery of the active ingredient on the seed reduces the potential impact to non-target organisms relative to foliar applied fungicides. Exposure is limited to the target crop resulting in a reduced pesticide load. Seed treatment is an effective method to reduce the risk of a pesticide having any harmful effect on the surrounding ecosystem.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The policy calls for the virtual elimination of Track 1 substances, which are those that meet all four criteria outlined in the policy: bioaccumulative, persistent (in soil and air), primarily a result of human activity, and toxic as defined in the *Canadian Environmental Protection Act*.

During the review process, ipconazole and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-05[4]. and evaluated against the Track 1 criteria (Appendix I, Table 26). The PMRA has reached the following conclusions:

- Ipconazole does not meet all Track 1 criteria, and is not considered a Track 1 substance.
- Ipconazole is not expected to form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants* maintained in the *Canada Gazette.*[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade ipconazole and the end-use products Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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[4] DIR99-05, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.

[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

[8] DIR2006-02, PMRA Formulants Policy.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for ipconazole is adequate to define the majority of toxic effects that may result from human exposure to ipconazole, with the exception of the inadequacy of dosing in the rat carcinogenicity study. In subchronic and chronic studies on laboratory animals, the primary target was the liver, lens (eyes), prostate, adrenals and thymus, with further effects on the endocrine organs and immune system at higher doses. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. However, an adequate dose was not achieved in the long-term rat study. Further toxicological data are requested and an additional uncertainty factor was incorporated into the risk assessment. There was evidence of increased susceptibility of the young in the developmental toxicity studies in rats and rabbits but not in the multi-generation rat reproductive toxicity study. Ipconazole is not considered to be a neurotoxicant in adult animals. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in plants and animals is adequately understood. The residue definition for enforcement is ipconazole. The residue definition for risk assessment is ipconazole and 1,2,4-T in animals and ipconazole, 1,2,4-T and the conjugate triazole metabolites (for example, TA, TAA and TP) in plants. The uses of ipconazole on cereal grains and the import of peanuts, soybeans and crops in crop subgroup 6C (dried shelled pea and bean, except soybean) do not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs to protect human health.

Commercial and on-farm seed treatment workers handling Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide and workers handling and planting treated seed are not expected to be exposed to levels of ipconazole that will result in an unacceptable risk when these products are used according to label directions. The personal protective equipment required on the product labels is adequate to protect workers treating seed and bagging treated seed as well as workers planting treated seed.

7.2 Environmental Risk

The primary environmental risk of the use of Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide, and Rancona Apex Fungicide as a seed treatment is to birds and mammals that may consume the treated seed. This risk was determined to be negligible if label statements regarding burial and cleanup of spilled treated seed are followed. Risk to other terrestrial and aquatic organisms, and non-target plants, is negligible based on low potential for exposure to these groups.

7.3 Value

The data submitted to register Rancona Apex Fungicide, Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide are adequate to demonstrate efficacy for use on cereal grain and corn seed in controlling or suppressing the proposed diseases and pathogens. The lowest effective rate for pests has been established and is supported by efficacy data. However, confirmatory efficacy data are required to demonstrate that Rancona Apex Fungicide is effective in controlling post-emergence damping-off caused by *Cochliobolus sativus* on wheat, barley, oats, rye and triticale, and that Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide are effective in controlling seed rot, damping-off and seedling blight caused by soil-borne *Fusarium* spp., and seed rot and damping-off caused by *Rhizoctonia solani* on sweet, field and popcorn.

7.4 Unsupported Uses

All uses were supported as proposed.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Ipconazole Technical Fungicide and Vortex FL Seed Treatment Fungicide, Rancona 3.8 FS Fungicide and Rancona Apex Fungicide, containing the technical grade active ingredient ipconazole, to protect against seedling and soil-borne diseases on small grain cereals and corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the registrant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The registrant will be required to submit the following information within the time frames indicated below.

Human Health

- A new rat cancer study at higher doses.
- Hormonal measurements in rats after at least 28-days of treatment.
- Toxicology studies being requested by other regulatory authorities.

- Additional supporting data consisting of dust off studies comparing the dust off potential of Vortex FL Seed Treatment Fungicide and Rancona 3.8 FS Fungicide on corn, and oats treated with Rancona Apex Fungicide, with that of the formulation and seed used in the surrogate studies used in the risk assessments, or an acceptable rationale, are requested. If the dust off studies demonstrate a higher dust off potential for corn treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide, or for oats treated with Rancona Apex Fungicide than canola or wheat treated with the surrogate compounds, further exposure data may be required.
- Freezer storage stability data.
- Data must be submitted within 3 years of this registration.

Value

- Three small-scale field, greenhouse and/or lab (Petri plate) trials confirming that Rancona Apex Fungicide is effective in controlling post-emergence damping-off caused by *C. sativus* on wheat, barley, oats, rye and triticale are required.

- Field trials on each pathogen (one on *Fusarium* spp. and two on *R. solani*) demonstrating that Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide are effective in controlling seed rot, damping-off and seedling blight caused by soil-borne *Fusarium* spp., and seed rot and damping-off caused by *R. solani* on sweet, field and popcorn are required.

- Data must be submitted within 3 years of this registration.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

List of Abbreviations

1,2,4-T	1,2,4-triazole
µg	microgram(s)
a.i.	active ingredient
ACTH	adrenocorticotropic hormone
AD	administered dose
ADI	acceptable daily intake
ARfD	acute reference dose
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CL	confidence limit
cm	centimetre(s)
d	day(s)
DAP	day(s) after planting
DM	dry matter
DMI	demethylation inhibitor
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in the test population)
dw	dry weight
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
F	female
F_1	First offspring generation; breeding adults descended from F_0 generation
F_2	Second offspring generation; descended from F_1 generation
FDA	United States Food and Drug Administration
FIR	food ingestion rate
FOB	functional observation battery
FSH	follicle stimulating hormone
g	gram(s)
GAP	good agricultural practices
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HD	high dose
HDPE	high density polyethylene
HPLC-MS	high performance liquid chromatography – mass spectroscopy
IUPAC	International Union of Pure and Applied Chemistry

kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD	low dose
LD_{50}	lethal dose 50%
LDPE	low density polyethylene
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
LOC	level of concern
LOQ	limit of quantitation
M	male
m	metre(s)
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score
MTDB	maximum theoretical dietary burden
MIS	maximum irritation score
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MRM	multi residue methods
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
NAFTA	North American Free Trade Agreement
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
ORO	Oil-red-O
Pa	Pascal
PAM	Pesticide Analytical Manual
PBI	plantback interval
PCPA	*Pest Control Product Act*
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	part(s) per billion
PPE	personal protective equipment
ppm	part(s) per million
RBC	red blood cells
RQ	risk quotient
SBI	sterol biosynthesis inhibitor
SN	solution

SU	suspension
T_{max}	time to peak concentration
T3	tri-iodothyronine
T4	thyroxine
TA	triazolylalanine
TAA	triazolylacetic acid
TP	triazolylpyruvate
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
US	United States
UV	ultraviolet
WBC	white blood cells

Appendix I Tables

Table 1 Residue Analysis in Soil

Matrix	Method type	Analyte	Method Type	LOQ	Reference
Soil	HPLC-MS	Active	HPLC-MS	0.001 ppm	PMRA 1368702

Table 2 Acute Toxicity of Ipconazole Technical Fungicide and Its Associated End-use Products (Rancona Apex Fungicide, Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Ipconazole Technical Fungicide				
Oral	Rat	$>LD_{50}$ = 888 mg/kg bw (95% CL = 663-1164 mg/kg bw) $>LD_{50}$ = 1338 mg/kg bw (95% CL = 1026-1740 mg/kg bw)	Moderate Toxicity	819497
Oral	Mouse	$>LD_{50}$ = 468 mg/kg bw (95% CL = 437-502 mg/kg bw) $>LD_{50}$ = 537 mg/kg bw (95% CL= 413-702 mg/kg bw)	Moderate Toxicity	1368575
Dermal	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	819498
Inhalation	Rat	LC_{50} > 1.88 mg/L	Slight Toxicity	819151
Skin irritation	Rabbit	MAS = 0/8 MIS = 0.33/8	Non-irritating	819501
Eye irritation	Rabbit	Washed: MAS = 6.11/110 MIS = 15.33/110 Unwashed: MAS = 4.78/110 MIS = 11.33/110	Mildly Irritating	819500
Skin sensitization (Maximization)	Guinea pig	Negative	Not a dermal sensitizer	1425837
Acute Toxicity of End-Use Product - Crusoe® MD Fungicide				
Oral	Rat	LD_{50} > 5000 mg/kg bw (limit)	Low Toxicity	1398171
Dermal	Rat	LD_{50} > 5000 mg/kg bw (limit)	Low Toxicity	1398173
Inhalation	Rat	LC_{50} > 2.07 mg/L (limit)	Low Toxicity	1398175
Skin irritation	Rabbit	MAS = 0.33/8 MIS = 3/8	Minimally Irritating	1398179
Eye irritation	Rabbit	MIS (1 hour) = 8/110 MAS (24, 48, 72 hours) = 2/110	Minimally Irritating	1398177

Study Type	Species	Result	Comment	Reference
Skin sensitization (Buehler)	Guinea pig	Negative	Not a dermal sensitizer	1398181
Acute Toxicity of End-Use Product - Rancona 3.8 FS Fungicide / Vortex FL Seed Treatment Fungicide				
Oral	Rat	>LD_{50} = 3666 mg/kg bw (95% CL = 3065-4514 mg/kg bw) >LD_{50} = 5284 mg/kg bw (95% CL = 4515-6570 mg/kg bw)	Low Toxicity	1394993
Dermal	Rat	$LD_{50} > 5000$ mg/kg bw (limit)	Low Toxicity	1394995
Inhalation	Rat	$LC_{50} > 2.59$ mg/L	Low Toxicity	1394997
Skin irritation	Rabbit	MAS = 0.33/8 MIS = 2.83/8	Minimally Irritating	1395001
Eye irritation	Rabbit	MAS = 0/110 MIS = 5.33/110	Minimally Irritating	1394999
Skin sensitization	Guinea pig	Negative	Not a dermal sensitizer	1395003

a MAS = maximum average score for 24, 28 and 72 hours

b MIS = maximum irritation score

Table 3 Toxicity Profile of Ipconazole Technical Fungicide

Study Type	Species	Results (mg/kg/day in M/F)	Reference
28-day dietary	Rat	Effect levels were not established, since this study was considered to be supplemental. Compound-induced effects in males at higher doses consisted of: decreased body weight/gains, food consumption; increased hyperchromatic erythrocytes; and decreased urinary volume and urinary electrolytes. Treatment-related effects in females occurred down to the lowest dose tested and included: decreased body weight/gains & food consumption; increased hyperchromatic erythrocytes; decreased urinary parameters & increased epithelial hyperplasia & hyperkeratosis in the nonglandular stomach. Increased lymphocytes, WBC; elevated liver enzymes; increased ulceration & subepithelial inflammation in the non-glandular stomach; and liver histopathology were observed at higher doses.	1464015
28-day dermal irritation	Rat	Systemic toxicity and dermal irritation: NOAELs =150 mg/kg bw/day LOAELs =1000 mg/kg bw/day, systemically, based on decreased body weight (M), body weight gain, food consumption and food conversion efficiency; increased adrenal weight (F) with associated diffuse cortical hypertrophy/hyperplasia (F); dermally, based on increased erythema, hyperplasia and thickening of treated skin	1368595

Study Type	Species	Results (mg/kg/day in M/F)	Reference
28-day inhalation	Rat	NOAEL = not established LOAEL = 31 mg/m^3 (equivalent to ~8 mg/kg bw/day), based on increased epithelial hyperplasia and/or metaplasia on epithelial surface of hard palate, larynx, nose/turbinate; increased inflammatory cells in mucosa of trachea (F) and lungs (M)	1368600, 1368601
28-day capsule (range-finding)	Dog (Beagle)	Effect levels were not established since this study was considered to be supplemental. Compound-related effects on body weight gain, eyes and liver were observed, with mortality, clinical signs and body weight loss occurring at the high dose.	1464019
90-day dietary	Mouse	NOAEL = 4.4/5.1 mg/kg bw/day M/F LOAEL = 20.2/25.4 mg/kg bw/day M/F, based on decreased body weight gain; increased hepatocyte vacuolation (M), increased generalised oil red-O staining in liver and decreased plasma cholesterol	1368619, 1368620
90-day dietary (1991)	Rat	NOAEL = 7.22/7.95 mg/kg bw/day M/F LOAEL = 29.89/32.50 mg/kg bw/day M/F, based on decreased body weight/gains (F), decreased food consumption (F); increased inorganic phosphate (F); thickened walls of the non-glandular stomach; erosion, hyperplasia of mucosa epithelium and hyperkeratosis of non-glandular stomach	1464014
90-day dietary (2003)	Rat	NOAEL = 5.8/7.0 mg/kg bw/day M/F LOAEL = 12.6/15.4 mg/kg bw/day M/F, based on increased corticomedullary mineralization in kidney (F), increased epithelial hyperplasia in the non-glandular stomach (M)	1368584, 1368587
90-day capsule	Dog (Beagle)	NOAEL = 2 mg/kg bw/day LOAEL = 10 mg/kg bw/day, based on increased reddening of the skin and increased anomaly of the lenticular fibres of the eyes	1368589
12-month dietary	Dog (Beagle)	NOAEL = 1.5 mg/kg bw/day LOAEL = 5 mg/kg bw/day, based on increased reddening of the skin (M/F) & decreased body weight gain (F)	1368591, 1368592
Carcinogenicity (18-month dietary)	Mouse	NOAEL = 1.9/2.3 mg/kg bw/day M/F LOAEL = 24.1/26.0 mg/kg bw/day M/F, based on increased generalized and centrilobular hepatocyte vacuolation; increased epithelial hyperplasia of the nonglandular stomach (F) **Dosing was considered adequate.**	1368623
Chronic/ Carcinogenicity (2-year dietary)	Rat	NOAEL = 9.0/7.3 mg/kg bw/day M/F LOAEL = 13.3/12.6 mg/kg bw/day M/F, based on decreased body weight gains and food efficiency (week 1) **Dosing was not considered adequate.**	1368601- 1368617

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Two-generation reproduction (range-finding)	Rat	Effect levels were not established, since this study was considered supplemental. Parental effects included decreased body weight and body weight gain at the high dose. Reproductive effects included increased ovary weight and decreased uterine/oviduct weight at the high dose, with the uterine/oviduct effect also occurring at the low and mid doses.	1368633
Two-generation reproduction	Rat	**Parental toxicity**: NOAEL = 2.2/2.6 mg/kg bw/day LOAEL = 7.2/8.4 mg/kg bw/day, based on decreased body weight and body weight gain in males with decreased food consumption in both genders during the F_1 pre-mating period; decreased body weight gain during the first week and decreased food consumption throughout lactation in F_0 females **Offspring toxicity:** NOAEL = 2.0 mg/kg bw/day LOAEL = 8.0 mg/kg bw/day, based on decreased body weight gain in F_1 offspring during the first week of lactation and the first four days post-weaning **Reproductive toxicity:** NOAEL = 22.0/8.4 mg/kg bw/day M/F LOAEL = Not established/25.5 mg/kg bw/day M/F, based on increased ovary weight, prolonged regular oestrus cycle, decreased implantation sites and decreased total offspring number	1368634- 1368640
Developmental toxicity (range-finding)	Rat	Effect levels not established, since this study was considered to be supplemental. Compound-related effects including clinical signs, body weight and food consumption effects were observed in maternal animals. The maximum tolerated dose was exceeded at the high dose. Treatment-related increased foetal resorptions and death and malformations (microphthalmia, kinky or short tail) were observed at higher doses.	1368642
Developmental toxicity	Rat	**Maternal:** NOAEL = 10 mg/kg w/day LOAEL = 30 mg/kg bw/day, based on decreased body weight gains and food consumption **Developmental:** NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day, based on decreased foetal weights and increased overall visceral and skeletal variations (dilatation of renal pelvis and/or ureter; left umbilical artery; lumbar ribs)	1368643

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Developmental toxicity (range-finding)	Rabbit	Effect levels not established, since this study was considered to be supplemental. Compound-related effects including body weight and food consumption effects were observed in maternal animals. The maximum tolerated dose was exceeded at high doses. Treatment-related increased foetal resorptions and death and malformations (microphthalmia, short, kinky or vestigial tails, general oedema) were observed at higher doses.	1368645
Developmental toxicity	Rabbit	**Maternal:** NOAEL = 10 mg/kg bw/day LOAEL = 50 mg/kg bw/day, based on decreased body weight gain, body weight loss, decreased food consumption and placental weight **Developmental:** NOAEL = 10 mg/kg bw/day LOAEL = 50 mg/kg bw/day, based on decreased foetal weights and increased malformations (splitting of parietal bone)	1368648
Reverse gene mutation assay	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA	Negative	1368651
Gene mutations in mammalian cells in vitro	Chinese hamster ovary cells (HGPRT locus)	Negative	1368653
In vitro mammalian chromosomal aberration	Chinese hamster lung fibroblast CHL/IU cells	Negative	1368655
In vivo mammalian cytogenetics (mouse micronucleus assay)	CD-1 mice	Negative	1368657
Bacteria DNA repair study in vitro	H17 (rec+) and M45 (rec-) of *Bacillus subtilis*	Negative	1368659

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Metabolism	Rat	**Absorption** Ipconazole is rapidly absorbed [~91-102% administered dose (AD) at low dose (LD; 2 mg/kg bw ^{14}C-benzyl methylene or ^{14}C-triazole label) and 71-92% at high dose (HD; 100 mg/kg bw ^{14}C-benzyl methylene label), both at 48 h] following oral gavage dosing in the rat. Absorption was decreased at HD suggesting saturation of the absorption kinetics. Time to peak concentration (T_{max}) for the LD ranged from ~2-6 h post-dosing in plasma and 1-6 h in whole blood, while that of the HD was slightly longer (~6-12 h post-dosing). The half-life of elimination was shorter in plasma than whole blood, suggesting the presence of radioactivity in RBCs. After repeat dosing (2 mg/kg bw radiolabelled ipconazole for 14 consecutive days), plasma/blood concentrations peaked 1 h post-dosing but failed to reach steady-state. The AUC increased 2-fold compared to the single dose suggesting further distribution into RBCs. **Distribution** At 120 h, high radioactivity was observed in the liver and RBCs, while intermediate levels were noted in the kidney and thyroid gland. No differences in organ distribution were noted between radiolabels, dose levels or single vs. repeat dosing groups. Residue levels at the high dose were 4-9-fold higher than the single dose. There was no evidence of bioaccumulation in the tissues. Expired air did not contain significant levels of ^{14}C-labelled volatiles. **Metabolism** Ipconazole was extensively metabolized mainly via hydroxylation and conjugation. Unchanged parent represented ~2.2% AD. Following low doses of radiolabelled ipconazole, the major of urinary metabolites (≤3.1% AD) remained unidentified in both sexes, except for the [^{14}C-triazole] males, which produced 1,2,4-triazole (6.9% AD). All other urinary metabolites accounted for ≤1.6% AD. No glucoronide and sulfate conjugates were present in urine after LD administration. A similar metabolic profile was observed after repeat dosing, however, an increase in the polar component suggested that induction of metabolism may have occurred to a limited extent after repeat dosing. The major faecal metabolite in both sexes was F22[b], which represented 5.0-7.2% AD at LD and 4.6-16.4% AD at HD. All other faecal metabolites accounted for <3.9% AD. The major metabolite in bile was a mixture of glucuronide conjugates (22%AD). The metabolic	1368661-1368665

Study Type	Species	Results (mg/kg/day in M/F)	Reference
		profile in bile-cannulated rats was similar between LD and HD groups, and between sexes. At the LD, B16 (a glucuronide conjugate) accounted for 22.0% and 16.8% AD in males and females, respectively. Other major metabolites included the polar fractions B1, B11 and B15a/b, which were identified as glucuronide conjugates. All other bile-derived metabolites each accounted for ≤3.8%AD. There were no major differences in metabolism between dose groups. **Excretion** Excretion of the LD and HD was rapid (93-94% AD at 48 hours) and occurred mostly via the faeces (78-82% AD at 48 h). The majority of the faecal radioactivity was due to biliary excretion (78-95% and 55-78% AD at LD and HD, respectively). Urinary excretion was virtually complete by 48 h and accounted for 12-24% AD. Females in all dose groups excreted slightly more radioactivity in the urine than males and retained slightly more in the carcass than males after high dose and repeat dose administration at 120 h (0.24% and 1.4% AD, respectively).	

a Effects observed in males as well as females unless otherwise reported

b Comprised of 1RS,2SR,5RS)-2-(4-chlorobenzyl)-5-(1-hydroxy-1-methylethyl-1-*1H-1,2,4-triazol-1-1ylmethyl)cyclopentanol and (1RS,2SR,5RS)-2-(4-chlorobenzyl)-5-[(1SR)-2-hydroxy-1-methylethyl]-1-(1H-1,2,4-triazol-1-ylmethyl)cyclopentanol)

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Ipconazole

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF^1 or Target MOE^2
Acute dietary, females aged 13-49	NOAEL = 10	Rabbit developmental toxicity	Decreased foetal weights; increased splitting of parietal bone (malformation) at 50 mg/kg bw/day	300
	ARfD = 0.033 mg/kg bw			
Chronic Dietary	NOAEL = 2	Co-critical studies: 12-month dog, 2-generation reproductive toxicity, 18-month mouse	12-month dog: decreased body weight gain (F); reddening of skin at 5 mg/kg bw/day 2-generation reproductive toxicity: decreased body weight, body weight gain, food consumption in parents & offspring at ~8 mg/kg bw/day 18-month mouse: liver & stomach histopathology at 24.1/26.0 mg/kg bw/day M/F	300

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF[1] or Target MOE[2]
	ADI = 0.0067 mg/kg bw/day			
Short- to intermediate-term Dermal	NOAEL = 10	Rabbit developmental toxicity	Decreased foetal weights and increased major malformations (splitting of parietal bone) at 50 mg/kg bw/day.	300
Short- to intermediate-term Inhalation	LOAEL = 8	28-day rat inhalation toxicity	Increased epithelial hyperplasia and/or metaplasia on epithelial surface of hard palate, larynx, nose/turbinate; increased inflammatory cells in mucosa of trachea (F) and lungs (M)	300

[1] Dietary scenarios

[2] Exposure scenarios

Table 5 Summary of Exposure and Risk Estimates for Commercial Seed Treatment Workers Treating Corn with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Mixer/loader - Closed Transfer - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	187.8	1.5	4.02	2 490
Inhalation	1.49	1.5	0.032	250 000
Coater - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	32.3	1.5	0.69	14 500
Inhalation	0.96	1.5	0.021	381 000
Bagger - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	20.4	1.5	0.44	22 700
Inhalation	0.11	1.5	0.0024	3 330 000
Shift Foreman - Long-sleeve shirt, long pants; chemical resistant gloves				
Dermal	97.5	1.5	2.09	4 790
Inhalation	0.50	1.5	0.011	727 000

[1] Commercial Seed Treatment Plant Worker Exposure Study with OFTANOL Seed Treatment on Canola.

[2] Based on an application rate of 2.5 g a.i./100 kg seed × 60 000 kg seed treated/day.

[3] Exposure (g/kg bw/day) = kg a.i. handled/day × unit exposure (g/kg a.i. handled) × 100% penetration/70 kg bw

[4] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 6 Summary of Unit Exposure Values for the Dean, 1993 Study

	Task	Number of Replicates (# indiv)	Mean Dermal Exposure µg/kg a.i. (st. dev.)	Mean Inhalation Exposure µg/kg a.i. (st. dev.)	Mean Total Exposure µg/kg a.i. (st. dev.)
Large facility	treater/bagger	4 (1)	262.78 (208.28)	14.87 (9.92)	277.65 (209.2)
	stacker/tagger	12 (3)	41.57 (29.97)	1.68 (0.79)	43.25 (30.15)
	forklift driver	4 (1)	12.02 (3.09)	1.21 (1.47)	13.22 (3.85)
	mixer/calibrator	1	364.08	0.17	364.24
Medium facility	bagger	6 (1)	88.19 (44.75)	61.03 (2917)	149.22 (54.27)
	tagger	6 (1)	113.77 (53.81)	145.71 (95.42)	259.48 (116.8)
	stacker1	6 (1)	62.06 (29.05)	11.87 (5.72)	73.93 (30.23)
	stacker2	6 (1)	49.44 (18.17)	10.85 (5.51)	60.29 (22.3)
	mixer/calibrator	1	7121.98	0.10	7122.08
	disassembly	1	482.35	33.18	515.53
Small facility	treater	6 (1)	**689.73** (172.27)	**245.74** (400.89)	935.47 (387.79)
	mixer/calibrator	1	220.27	0.09	220.36
	disassembly	1	105.02	0.47	105.49

Table 7 Summary of Exposure and Risk Estimates for Commercial Workers Treating Cereal Seed with Rancona Apex Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Clothing Scenario: long-sleeved shirts, long pants, chemical resistant gloves				
Dermal	689.73	1.6	15.76	635
Inhalation	245.74	1.6	5.62	1423

[1] Commercial Treater Exposure Study with Baytan 312 FS Seed Treatment on Grain Seeds (Dean, 1993).

[2] Based on an application rate of 2.0 g a.i./100 kg seed × 80 000 kg seed treated/day.

[3] Exposure (g/kg bw/day) = kg a.i. handled per day × unit exposure (g/kg a.i. handled) × 100% penetration/70 kg bw

[4] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 8 Summary of Exposure and Risk Estimates for On-Farm Workers Treating and Planting Cereal Seed Treated with Rancona Apex Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Dermal	111.84	0.27	0.43	23 200
Inhalation	20.6	0.27	0.079	101 000

[1] On-farm Treater and Planter Exposure Study with Vitaflo 280 Fungicide on Cereal Seeds.

[2] Based on an application rate of 2.0 g a.i./100 kg seed × 13 500 kg seed treated and planted/day.

[3] Exposure (g/kg bw/day) = kg a.i. handled per day × unit exposure (g/kg a.i. handled) × 100% penetration/70 kg bw

[4] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 9 Summary of Exposure and Risk Estimates for Workers Planting Corn Seed Treated with Vortex FL Seed Treatment Fungicide or Rancona 3.8 FS Fungicide

Subpopulation and Route	Unit Exposure[1] (g/kg a.i. handled)	Amount a.i. handled[2] (kg)	Exposure [3] (g/kg bw/day)	MOE[4]
Dermal	424.2	0.034	0.206	48 500
Inhalation	1.11	0.034	0.000535	14 950 000

[1] Seed Planting Worker Exposure Study with Oftanol Seed Treatment on Canola.

[2] Based on an application rate of 2.5 g a.i./100 kg seed × 1350 kg seed planted/day.

[3] Exposure (g/kg bw/day) = kg a.i. handled per day × unit exposure (g/kg a.i. handled) × 100% penetration/70 kg bw

[4] Based on an oral NOAEL of 10 mg/kg bw/day for dermal exposure and an inhalation LOAEL of 8 mg/kg bw/day. The target for both dermal and inhalation exposure is 300.

Table 10 Residue Analysis in Plant Matrices

Method ID	Analyte	Method Type	LOQ	Matrices	Reference
Plant					
AC 3020	Ipconazole	Enforcement	0.01	Wheat, corn, cotton seed, peanut nutmeat and soybean	1675044
AC 3020A					1670246
KRA/119-03R	Ipconazole, TA, TAA and TP	Data-gathering	0.01	Barley, corn, cotton, soybean and wheat	1398226, 1398230
KRA/0134-01R	Ipconazole, TA, TAA, TP and 1,2,4-T	Data-gathering	0.01	Peanuts	1398227, 1398229

Table 11 Residue Chemistry Summary Tables

NATURE OF THE RESIDUE IN SOYBEAN (SEED TREATMENT)			PMRA # 1368673, 1368675
Matrix	Soybean (Variety: Asgrow A6101)		
Test Site	Outdoor plots		
Treatment	Seed treatment		
Application Timing	Not applicable		
Rate	1.5, 2.5 or 10.0 g a.i./100 kg seed[1]		
End-use product	[triazole-3,5-^{14}C]-ipconazole or [benzyl methylene-^{14}C]-ipconazole (formulation not stated)		
Matrix	PHI (days)	[triazole-3,5-^{14}C]-ipconazole TRR (ppb)	[benzyl methylene-^{14}C]-ipconazole TRR (ppb)
Forage	63	7.66	0.45
Hay	90	22.39	1.33
Seed	168	59.57	0.26
[1]Characterization and identification was only completed for the 10.0 g a.i./100 kg seed treatment rate.			

Metabolites Identified	Major Metabolites (> 10% of the TRR)	
Radiolabel Position	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole
Hay	TP	Due to low TRR, no residues were identified in any of the matrices.
Seed	TP	
	Minor Metabolites (< 10% of the TRR)	
Forage	No minor metabolites identified.	
Hay		
Seed		

NATURE OF THE RESIDUE IN WINTER WHEAT (SEED TREATMENT)			**PMRA # 1368673, 1368678**
Matrix	Winter wheat (Variety: Coker 9543)		
Test Site	Outdoor plots		
Treatment	Seed treatment		
Application Timing	Not applicable		
Rate	1.5, 2.5 or 10.0 g a.i./100 kg seed[1]		
End-use product	[triazole-3,5-^{14}C]-ipconazole or [benzyl methylene-^{14}C]-ipconazole (formulation not stated)		
Matrix	PHI (days)	[triazole-3,5-^{14}C]-ipconazole TRR (ppb)	[benzyl methylene-^{14}C]-ipconazole TRR (ppb)
Forage	136	12.56	1.48
Hay	157	23.95	1.43
Straw	207	20.38	5.10
Grain	207	38.09	0.50
[1] Characterization and identification was only completed on wheat grain for the 10.0 g a.i./100 kg seed treatment rate.			
Metabolites Identified	Major Metabolites (> 10% of the TRR)		
Radiolabel Position	[triazole-3,5-^{14}C]-ipconazole		[benzyl methylene-^{4}C]-ipconazole
Grain	TP		Due to low TRR, no residues were identified in any of the matrices.
	Minor Metabolites (< 10% of the TRR)		
Grain	No minor metabolites identified.		

NATURE OF THE RESIDUE IN WINTER WHEAT (SEED TREATMENT)		**PMRA # 1368697**
Matrix	Winter Wheat (Variety: Jagger)	
Test Site	Outdoor barrels	
Treatment	Seed treatment	
Application Timing	Not applicable	
Rate	2.5 g a.i./100 kg seed or 20 g a.i./100 kg seed[1]	
End-use product	[triazole-3,5-^{14}C]-ipconazole (formulated as a wettable powder)	
Matrix	PHI (days)	[triazole-3,5-^{14}C]-ipconazole TRR (ppb)
Forage	188	15.4
Hay	220	22.0
Straw	241-266	31.5

Grain	266	23.7
[1] Characterization and identification was only completed on wheat grain for the 20.0 g a.i./100 kg seed treatment rate.		
Metabolites Identified	Major Metabolites (> 10% of the TRR)	
Radiolabel Position	[triazole-3,5-^{14}C]-ipconazole	
Grain	TP	
	Minor Metabolites (< 10% of the TRR)	
Grain	No minor metabolites identified.	

NATURE OF THE RESIDUE IN SPRING WHEAT (SEED TREATMENT)	**PMRA # 1368695**

Matrix	Spring wheat (Variety: Alsen)
Test Site	Outdoor plots
Treatment	Seed treatment
Application Timing	Not applicable
Rate	2.5 or 25 g a.i./100 kg seed
End-use product	[triazole-3,5-^{14}C]-ipconazole or [benzyl methylene-^{14}C]-ipconazole (formulated as a wettable powder)

Matrix	PHI (days)	[triazole-3,5-^{14}C]-ipconazole TRR (ppb)		[benzyl methylene-^{14}C]-ipconazole TRR (ppb)	
		2.5 g a.i./100 kg seed	25 g a.i./100 kg seed	2.5 g a.i./100 kg seed	25 g a.i./100 kg seed
Forage	49	8.16	46.1	2.51	17.7
Hay	69	14.6	69.3	5.74	50.8
Straw	104-110	38.7	323	20.9	96.0
Grain	101-110	23.7	156	0.775	1.88

Metabolites Identified	Major Metabolites (> 10% of the TRR)			
Radiolabel Position	[triazole-3,5-^{14}C]-ipconazole		[benzyl methylene-^{14}C]-ipconazole	
	2.5 g a.i./100 kg seed	25 g a.i./100 kg seed	2.5 g a.i./100 kg seed	25 g a.i./100 kg seed
Forage	TP, TAA, TA	TAA, TA	Ipconazole, OH-ipconazole-glycosides, tert-OH-isopropyl-ipconazole	Ipconazole, OH-ipconazole-glycosides, tert-OH-isopropyl-ipconazole
Hay	TP, TAA, TA	TP, TAA, TA		
Straw	TAA, TA, OH-ipconazole-glycosides, tert-OH-isopropyl-ipconazole	TP, TAA, TA		
Grain	TAA, TA	TAA, TA	Due to low TRR, no residues were identified in any of the matrices.	
	Minor Metabolites (< 10% of the TRR)			
	[triazole-3,5-^{14}C]-ipconazole		[benzyl methylene-^{14}C]-ipconazole	
	2.5 g a.i./100 kg seed	25 g a.i./100 kg seed	2.5 g a.i./100 kg seed	25 g a.i./100 kg seed
Forage	Ipconazole, OH-ipconazole-glycosides, tert-OH-isopropyl-ipconazole		No minor metabolites identified.	
Hay				
Straw	Ipconazole, TP	Ipconazole, OH-ipconazole-glycosides, tert-OH-isopropyl-ipconazole		

Grain	TP	TP	

Plant Metabolism

The results obtained from winter wheat and soybean metabolism studies only confirmed the identity of triazolylpyruvate, but the ion signals for TA and TAA were not observed. There were several other minor peaks that were not further identified and characterized at the time due to analytical methodology limitations. However, in the spring wheat study, the necessary steps of extraction and fractionation were taken to isolate the common triazole metabolites. The spring wheat study is more contemporary and they were able to demonstrate the presence of common triazole metabolites (TA, TAA and TP).

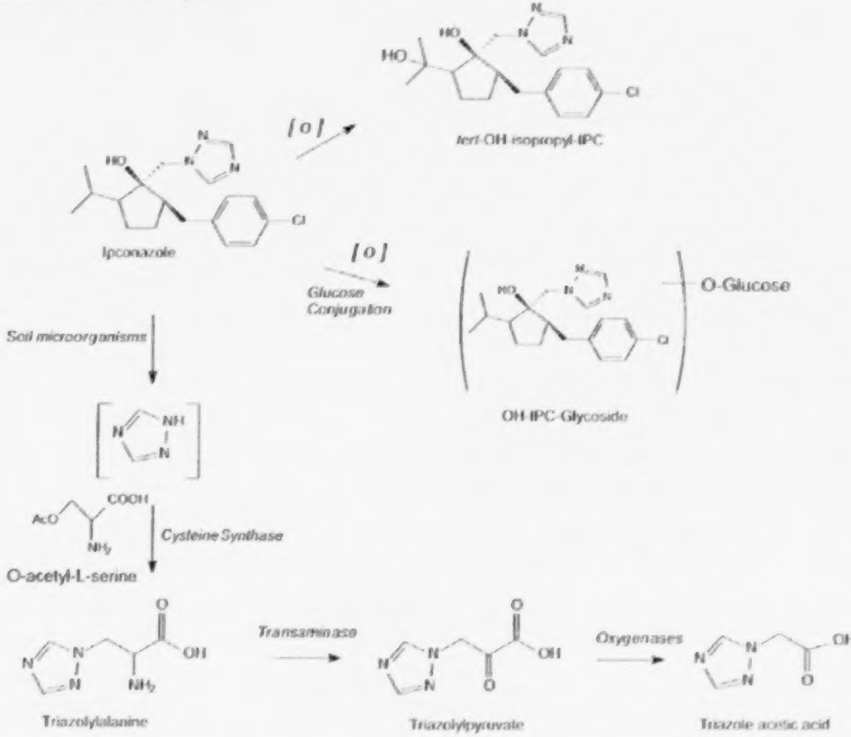
The pathway elucidated in the spring wheat study is indicative of the expected plant metabolism of other triazole compounds. In plants, 1,2,4-T is rapidly conjugated with serine to form TA which can then be oxidized to form TAA. Based on the spring wheat study, metabolism of ipconazole in wheat is proposed to proceed via one of three pathways: (1) degradation of ipconazole to triazole by soil microorganisms, which is then metabolized by wheat into TA, TP, and TAA; or (2) hydroxylation followed by glucose conjugation to form hydroxy-ipconazole-glycosides; or (3) hydroxylation to form tert-hydroxy-isopropyl-ipconazole.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – WHEAT, LETTUCE AND CARROT				**PMRA # 1398279**	
Radiolabel Position		[triazole-3,5-^{14}C]-ipconazole		[benzyl methylene-^{14}C]-ipconazole	
Test site		Container pots of sandy loam soil in an environmentally controlled room.			
Formulation used for trial		[triazole-3,5-^{14}C]-ipconazole or [benzyl methylene-^{14}C]-ipconazole (formulation not stated)			
Application rate and timing		One foliar application to bare soil at 216 g a.i./ha; 30 days, 120 days and 365 days prior to sowing wheat, lettuce and carrots.			
Metabolites Identified		Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Matrix	PBI (days)	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole
Wheat forage	30	Ba-2, TAA, TA	—	Ba-1, Ipconazole	—
	120	TAA, TA	—	Ba-1	—
	365	TAA, TA	Ba-1	Ba-1, Ba-2	—
Wheat hay	30	TAA, TA	Ba-1, KNF-317-M-1	KNF-317-M-1, Ba-1, Ba-2	Ba-2
	120	TAA, TA	—	—	Ipconazole, Ba-1, Ba-2, KNF-317-M-1
	365	TAA, TA	Ba-1, Ba-2	Ipconazole, Ba-1, Ba-2, KNF-317-M-1	KNF-317-M-1
Wheat straw	30	TAA, TA	Ba-1	KNF-317-M-1, Ba-1, Ba-2	Ba-2, KNF-317-M-1
	120	TA, TAA	—	Ipconazole, Ba-1, Ba-2, KNF-317-M-1	Ipconazole, Ba-1, Ba-2, KNF-317-M-1
	365	TAA, TA	Ipconazole, Ba-1, Ba-2	KNF-317-M-1	KNF-317-M-1
Wheat grain	30	TAA, TA	—	—	—
	120	TA	—	TAA	—
	365	TAA, TA	—	Ipconazole, Ba-1, Ba-2, KNF-317-M-1	—

Carrot tops (normal harvest)	30	Ba-1, TAA, TA	Ba-1	—	Ba-2
	120	TAA, TA	Ba-1	—	Ba-2
	365	TAA, TA	Ba-1	Ba-1, Ba-2, KNF-317-M-1	Ba-2
Carrot roots (normal harvest)	30	TA	—	TAA	—
	120	TA	—	TAA	—
	365	TAA, TA	—	Ba-1, Ba-2, KNF-317-M-1	—
Lettuce (normal harvest)	30	TAA, TA	—	KNF-317-M-1, Ba-1, Ba-2, Ipconazole	—
	120	TAA, TA	—	—	—
	365	TAA, TA	—	Ba-1, Ba-2	—

Residues of ipconazole were less than 0.01 ppm in secondary crops at all plantback intervals following one soil directed application of [^{14}C C-benzylmethylene] or [^{14}C -triazole]-ipconazole]. Therefore, quantifiable residues of ipconazole are not likely to be found in any rotational crop commodities following planting of seed treated with ipconazole at the maximum proposed rate.

Proposed metabolic scheme in plants



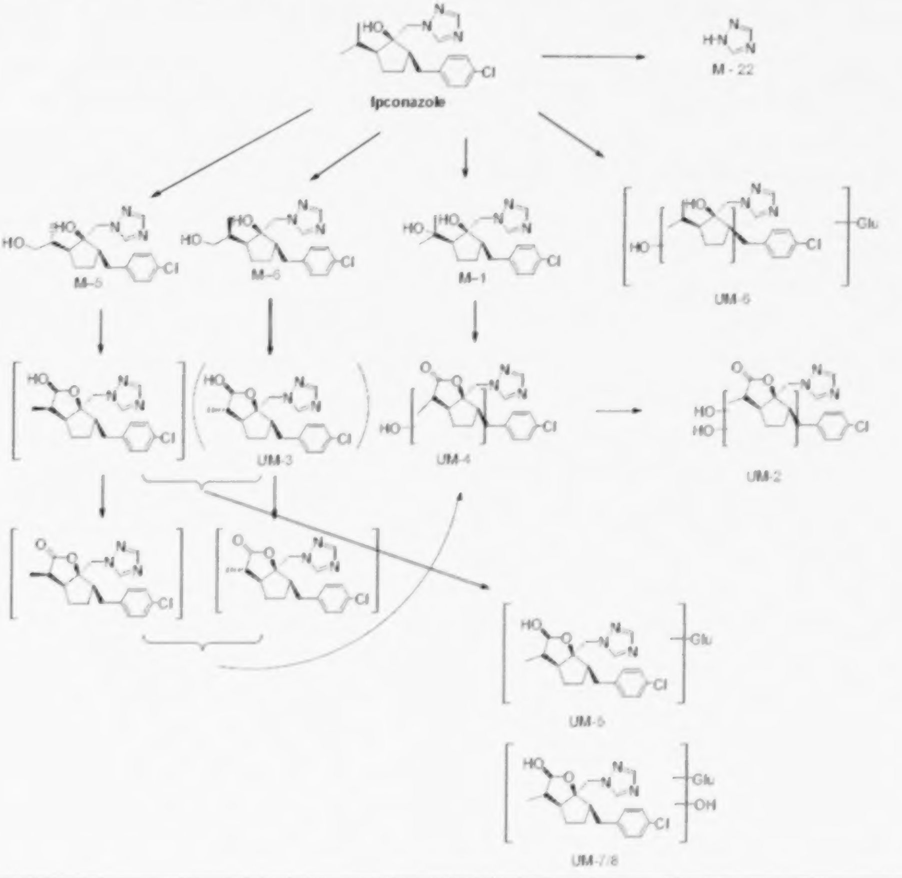
NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA # 1368669, 1368670**

The metabolism of [^{14}C -triazole]-ipconazole (specific activity 56 mCi/mmole) and [^{14}C -benzylmethylene] ipconazole (specific activity 58 mCi/mmole) in lactating goats was investigated. Lactating goats were dosed orally, once daily, via capsule equivalent to 10.6 and 12.6 ppm in the feed for 5 consecutive days for the benzylmethylene- and triazole-treated goats, respectively. Milk samples were collected twice daily, urine and feces were collected once daily. The goats were sacrificed ca. 23 hrs after the last dosage, and muscle (foreleg and rump), fat (perirenal, omental subcutaneous), liver, kidneys were collected.

Matrices	% of Administered Dose	
	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole
Urine and feces	81.9	92.5
Muscle	—	—
Fat	—	—
Kidney	0.03	0.01
Liver	0.82	0.31
Milk	0.12	0.09

Metabolites identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole	[triazole-3,5-^{14}C]-ipconazole	[benzyl methylene-^{14}C]-ipconazole
Muscle, foreleg	1, 2, 4-T, unknowns/others	—	Ipconazole	—
Muscle, rump	1, 2, 4-T, unknowns/others	—	Ipconazole	—
Kidney	Unknowns/others	Unknowns/others	Ipconazole, KNF-317-M-6, KNF-317-M-5	Ipconazole, KNF-317-M-6, KNF-317-M-5
Liver	UM-4, Unknowns/others	Ipconazole, unkowns/others	Ipconazole, KNF-317-M-6, KNF-317-M-5	KNF-317-M-6
Milk	1, 2, 4-T, unknowns/others	—	Ipconazole	—

Proposed Metabolic Scheme in Lactating Goats



Ruminant Metabolism

It is proposed that ipconazole is extensively metabolized in the goat to numerous components via metabolic pathways including glucuronidation (urine and feces) and hydroxylation (liver, kidney, urine and feces). Evidence of ring cleavage to the free triazole (1,2,4 – triazole) was observed in muscle and milk. Analysis of the cis:trans isomer ratios of ipconazole in the extracts of liver indicated there may have been some isomer specific metabolism (triazole label).

STORAGE STABILITY – PEANUT NUTMEAT, WHEAT AND CORN	PMRA# 1398233, 1398234, 1398235

Residues of ipconazole (in all matrices studied), TA (all matrices expect wheat straw after 6 months of frozen storage), TAA (all matrices studied) and TP (grain only) are considered stable for at least 13 months of frozen storage. Corrections were applied as necessary for the decline of TP residues in/on wheat forage, hay and straw and in/on maize cobs, forage and straw; and for TA residues in/on wheat straw when stored after 6 months of frozen storage.

CROP FIELD TRIALS ON BARLEY	**PMRA# 1398255**

GAP: Maximum seasonal rate of 2 g a.i./100 kg seed.

A total of eight supervised residue trials were conducted in 2005 on barley grown from treated seed in NAFTA representative growing regions (5, 5B, 7 and 14). Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Barley forage was harvested 64-102 days after planting (DAP) and grain and straw were harvested 90-131 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in barley hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Barley Hay	2.5	64-102	14	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	102	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Barley Straw	2.5	90-131	14	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	131	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Barley Grain	2.5	91-131	14	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	131	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON SPRING BARLEY	**PMRA# 1398260**

GAP: Maximum seasonal rate of 2 g a.i./100 kg seed.

A total of three supervised residue trials were conducted in 2006 on spring barley grown from treated seed in NAFTA representative growing region 14. Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed. Barley forage was harvested 67-78 DAP; grain and straw were harvested 85-103 DAP. Residues of ipconazole, TA and TAA were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in spring barley hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Barley Hay	2.5	67-78	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Barley Straw	2.5	85-103	4	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Barley Grain	2.5	85-103	4	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON BARLEY	**PMRA# 1398253**

US GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of three US supervised residue trials were conducted in 2005 on barley grown from treated seed in NAFTA representative growing regions (5, 7 and 11). Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Barley hay was harvested 52-79 DAP and grain and straw were harvested 86-135 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in barley hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Barley hay	0.0025	52-79	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	0.0125		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Barley grain	0.0025	86-135	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	0.0125		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Barley straw	0.0025	86-135	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	0.0125		6	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON CORN

PMRA# 1398275

GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of six supervised residue trials were conducted in 2006 on corn grown from treated seed in NAFTA representative growing region 5. Vortex FL was applied to seeds at an application rate of 2.5 g a.i./100 kg seed. Corn forage was harvested 90-127 DAP and grain and stover were harvested 112-143 DAP. Samples were analysed for residues of ipconazole only using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in corn forage, grain and stover.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Corn Forage	2.5	90-127	12	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Corn Grain	2.5	112-143	12	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Corn Stover	2.5	112-143	12	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON FIELD CORN

PMRA# 1398262

US GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of three US supervised residue trials were conducted in 2005 on field corn grown from treated seed in NAFTA representative growing region 5. Vortex FL was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Corn forage was harvested 84-89 DAP and grain and stover were harvested 115-129 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in corn forage, grain and stover.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Field corn forage	12.5	84-89	6	<0.01	<0.01	<0.01	0.01	0.01	NA[4]
Field corn grain	12.5	115-129	6	<0.01	<0.01	<0.01	0.01	0.01	NA
Field corn stover	12.5	115-119	6	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON COTTON

PMRA# 1398273

US GAP: Maximum seasonal rate of 10 g a.i./100 kg seed.

A total of three US supervised residue trials were conducted in 2005 on cotton grown from treated seed in NAFTA representative growing regions (4, 8 and 10). Vortex FL was applied to seeds at an application rate of 10 g a.i./100 kg seed and 50 g a.i./100 kg seed. Cotton seed was harvested 147-196 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in cotton seed. Due to low residue levels at the 50 g a.i./100 kg seed treatment, samples were not analysed at the 10 g a.i./100 g seed treatment.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Cotton seed	50	148-196	4	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON PEANUTS

PMRA# 1398271

US GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of three US supervised residue trials were conducted in 2005 on peanuts grown from treated seed in NAFTA representative growing regions (5 and 6). Vortex FL was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Peanut nutmeat was harvested 113-150 DAP. Residues of ipconazole, TA, TAA, TP and 1, 2, 4-triazole were analysed using LC-MS/MS method, KRA/0134-01R. No quantifiable residues of ipconazole were observed in peanut nutmeat. Due to low residue levels at the 12.5 g a.i./100 kg seed treatment, samples were not analysed at the 2.5 g a.i./100 g seed treatment.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Peanut nutmeat	12.5	113-150	6	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON SOYBEANS

PMRA# 1398267

US GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of three US supervised residue trials were conducted in 2005 on soybeans grown from treated seed in NAFTA representative growing region 5. Vortex FL was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Soybean forage was harvested 33-45 DAP, soybean hay was harvested 49-55 DAP and soybean seed was harvested 102-129 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in soybean forage, hay and grain.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Soybean forage	2.5	33-45	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Soybean hay	2.5	49-55	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Soybean seed	2.5	102-129	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON WINTER AND SPRING WHEAT

PMRA# 1398245 and 1398249

US GAP: Maximum seasonal rate of 2.5 g a.i./100 kg seed.

A total of four US supervised residue trials were conducted in 2005-2006 on winter and spring wheat grown from treated seed in NAFTA representative growing regions (5, 6 and 7). Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Spring wheat forage was harvested 29-30 DAP, winter wheat forage was harvested 98-220 DAP, spring wheat hay was harvested 50-75 DAP and winter wheat hay was harvested 160-243 DAP. Wheat straw and grain were harvested 94-99 DAP for spring wheat and 195-227 DAP for winter wheat. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in wheat forage, hay, grain and straw, irrespective of the variety of wheat.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Wheat forage	2.5	29-220	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Wheat hay	2.5	50-243	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA

Wheat straw	2.5	94-277	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA
Wheat grain	2.5	94-277	6	<0.01	<0.01	<0.01	0.01	0.01	NA
	12.5		6	<0.01	<0.01	<0.01	0.01	0.01	NA

CROP FIELD TRIALS ON SPRING WHEAT **PMRA# 1398237**

GAP: Maximum seasonal rate of 1.5 g a.i./100 kg seed.

A total of eight supervised residue trials were conducted in 2005 on spring wheat grown from treated seed in NAFTA representative growing regions (7, 7A and 14). Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Spring wheat forage was harvested 28-40 DAP, spring wheat hay was harvested 68-102 DAP and spring wheat straw and grain were harvested 105-133 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in wheat forage, hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Forage	2.5	28-40	16	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	40	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Hay	2.5	68-102	16	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	102	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Straw	2.5	105-133	16	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	133	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Grain	2.5	105-133	16	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	133	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON SPRING WHEAT **PMRA# 1398251**

GAP: Maximum seasonal rate of 1.5 g a.i./100 kg seed.

A total of three supervised residue trials were conducted in 2006 on spring wheat grown from treated seed in NAFTA representative growing region 14. Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed. Spring wheat forage was harvested 35-49 DAP, spring wheat hay was harvested 70-86 DAP and spring wheat straw and grain were harvested 87-113 DAP. Residues of ipconazole, TA and TAA were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in wheat forage, hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Wheat Forage	2.5	35-49	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Hay	2.5	70-86	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Straw	2.5	87-113	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Grain	2.5	87-113	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON WINTER WHEAT **PMRA# 1398247**

GAP: Maximum seasonal rate of 1.5 g a.i./100 kg seed.

A total of three supervised residue trials were conducted in 2005 on winter wheat grown from treated seed in NAFTA representative growing region 5. Ipconazole 5MD was applied to seeds at an application rate of 2.5 g a.i./100 kg seed and 12.5 g a.i./100 kg seed. Winter wheat forage was harvested 203-219 DAP, wheat hay was harvested 242-267 DAP and wheat straw and grain were harvested 279-294 DAP. Residues of ipconazole, TA, TAA and TP were analysed using LC-MS/MS method, KRA/119-02R. No quantifiable residues of ipconazole were observed in wheat forage, hay, grain and straw.

Commodity	Total Applic. Rate (g a.i./100 kg seed)	DAP (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Wheat Forage	2.5	203-219	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA[5]
	12.5	203	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Hay	2.5	242-267	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	242	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Straw	2.5	267-294	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	279	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Wheat Grain	2.5	267-294	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	12.5	279	2	<0.01	<0.01	<0.01	<0.01	<0.01	NA

PROCESSED FOOD AND FEED — **PMRA # 1398277**

Chemtura Canada Co. requested a waiver for completion of further processed food and feed residue data. Within the submitted crop field trials, exaggerated rate treatments (approximately 8-fold proposed Canadian GAP) were also conducted. All of the exaggerated rate trials did not yield any residues of ipconazole greater than LOQ (0.01 ppm). Therefore the waiver for completion of processing studies can be supported. Processing studies may be required if the use pattern and/or the residue pattern for ipconazole changes (i.e., foliar application).

LIVESTOCK FEEDING — **PMRA # 1398277**

Chemtura Canada Co. requested a waiver for completion of a livestock feeding study. Based on the results from the goat metabolism study anticipated residues were calculated and are < 0.00011 ppm. As well ipconazole residues were below the LOQ of 0.01 ppm in all feed commodities. Therefore, quantifiable residues of ipconazole are not anticipated in animal matrices. At this time the waiver to conduct an ipconazole feeding study can be supported. However, a feeding study may be required if the use pattern (i.e., foliar application) changes.

Livestock Maximum Theoretical Dietary Burden and Anticipated Residues.

Calculation of Livestock Anticipated Dietary Burden in Beef, Dairy, Poultry and Swine

				% Diet				**Maximum Theoretical Dietary Burden (ppm)**			
Feedstuff	Type	Residue (ppm)	% DM	Beef	Dairy	Poultry	Swine	Beef	Dairy	Poultry	Swine
Wheat forage	R	0.01	25	25	40	—	—	0.01	0.016	—	—
Field Pea Vine	R	0.01	25	15	5	—	—	0.006	0.002	—	—
Peanut meal	P	0.01	85	15	15	—	5	0.002	0.002	—	0.001
Field corn milled byproducts	C	0.01	85	35	25	—	—	0.004	0.003	—	—
Sweet corn cannery waste	C	0.01	30	10	10	—	—	0.003	0.003	—	—
Sorghum grain	C	0.01	86	—	5	—	—	—	0.001	—	—
Cotton meal	P	0.01	89	—	—	20	15	—	—	0.002	0.002
Barley grain	C	0.01	88	—	—	70	60	—	—	0.007	0.006
Field corn grain	C	0.01	88	—	—	10	20	—	—	0.001	0.002
Totals				100	100	100	100	0.025	0.027	0.010	0.010

R (roughage); C (carbohydrates); P (protein).

Calculation of the Anticipated Residues for Dietary Exposure Assessment					
Matrix	**Maximum Total Residues[1] (ppm)**	**Feeding level (ppm)**	**Transfer Coefficient[2]**	**MTDB (ppm)**	**Anticipated Residues[3] (ppm)**
Whole milk	<0.001	12.6	0.000079	0.027	0.000002
Goat kidney	0.005		0.000396	0.025	0.00001
Goat muscle	<0.001		0.000079		0.000002
Goat liver	0.056		0.004444		0.00011
Goat fat	<0.01		0.000793		0.0002

[1] Maximum Total Residues = ipconazole.

[2] Transfer coefficient is calculated as residue level-to-feed ratios.

[3] Anticipated residues for dietary exposure assessment = Transfer coefficient × anticipated dietary burden.

Table 12 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (cereals)**	Ipconazole
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops**	Ipconazole, 1,2,4-Triazole and the conjugated triazole metabolites (e.g., Triazolylalanine, Triazolylacetic acid and Triazolylpyruvate)
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops cannot be determined, because only wheat and soybean were investigated.
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	Ipconazole
RESIDUE DEFINITION FOR RISK ASSESSMENT	Ipconazole and 1,2,4-Triazole
METABOLIC PROFILE IN ANIMALS **(goat, rat)**	The metabolic profile was similar in animals investigated.
FAT SOLUBLE RESIDUE	No

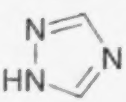
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Basic chronic non-cancer dietary risk **ADI = 0.0067 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.029 μg a.i./L**	General Population	0.7	0.7
	All Infants (<1 year old)	0.8	0.8
	Children 1-2 years old	1.6	1.6
	Children 3-5 years old	1.7	1.7
	Children 6-12 years old	1.2	1.2
	Youth 13-19 years old	0.9	0.9
	Adults 20-49 years old	0.6	0.6
	Adults 50+ years old	0.4	0.4
	Females 13-49 years old	0.5	0.6
Basic acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 0.12 μg a.i./L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
ARfD = 0.033 mg/kg bw/day	Females 13–49 years	0.25	0.25

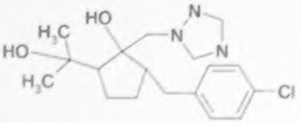
Table 13 Fate and Behaviour in the Environment

Property	Test substance	Value	Transformation products	Comments	Reference
Terrestrial environement					
Abiotic transformation					
Hydrolysis	N/A	N/A	N/A	N/A	
Phototransformation on soil	N/A	N/A	N/A	N/A	
Biotransformation					
Biotransformation in aerobic soil	ipconazole	DT_{50} range 180 d to 750 d DT_{90} range 600 d to 1100 d (20°C), and 2000 d (10°C)	No major transformation products	Persistent	1368719 1368721 819505, 874210, 874150
Biotransformation in anaerobic soil	ipconazole	DT_{50} = 779 d DT_{90} = 2587 d	No major transformation products	Persistent	1368723
Mobility					
Adsorption / desorption in soil	ipconazole	K_{oc} range 2029 to 3492 K_{oc} Freundlich = 1714	No major transformation products	Low mobility to immobile	819507, 874159 1368729

Property	Test substance	Value	Transformation products	Comments	Reference
Soil column leaching	No study submitted. Waiver request, based on limited potential for leaching as exhibited in the adsprotion/desoprtion studies, considered acceptable.				
Volatility	No study submitted. Waiver request, based on ipconazole having a low volatility, considered acceptable.				
Aquatic environment					
Abiotic transformation					
Hydrolysis	ipconazole	Does not hydrolyse	No major transformation products	Stable	819506, 874157, 874158, 874148
Phototransformation in water	ipconazole	Half life = 34 d continuous irradiation Predicted half life = 64 d based on non-continuous irradiation	No major transformation products	stable	1368710
Aerobic aquatic biotransformation	Not required and not submitted.				
Anaerobic aquatic biotransformation	Not required and not submitted.				

Table 14 Major and Minor Environmental Transformation Products of Ipconazole

Code	Chemical name	Chemical structure	Study	Max % Applied radioactivity	% radioactivity at study end (study length)
I-09	1 H- 1,2,4-triazole		Aerobic soil	Average 11.9% (day 31)	Average 7% (365 d)
			Anaerobic soil	Not provided	Not provided
			Soil photolysis	N/A	N/A
			Aqueous photolysis	Not provided	Not provided
			Hydrolysis	Not provided	Not provided
			Aerobic aquatic	N/A	N/A
			Anaerobic aquatic	N/A	N/A
			Field studies	Not provided	Not provided

Code	Chemical name	Chemical structure	Study	Max % Applied radioactivity	% radioactivity at study end (study length)
KNF-317-M-1	1 S, 2R, 5S)-2-(4-chlorobenzyl)-5-(1 -hydroxy- 1 -methylethyl)- 1 -(1 H-1,2,4-triazol- 1 -ylmethyl)cyclopentanol	 HO H₃C HO H₃C N N N Cl	Aerobic soil	**Study 1** 14C-Triazole: Portion of 3.8% (122) 14benzyl: Portion of 3.5% (90) **Study 2 (20°C)** 2.1% (59) 1.0% (90) 3.6% (90) **(10°C)** **1.1% (90)**	**Study 1** 14C-Triazole: Portion of 3.7% (230) 14benzyl: Portion of 4.4% (230) **Study 2 (20°C)** 2.8% (122) 1.7% (122) 2.9% (120) **(10°C)** **1.2% (122)**
			Anaerobic soil	14C-Triazole: 0.7% (37) 14Cbenzyl: 0.8% (60)	14C-Triazole: 0.6% (120) 14Cbenzyl: 0.6% (120)
			Soil photolysis	N/A	N/A
			Aqueous photolysis	Not provided	Not provided
			Hydrolysis	Not provided	Not provided
			Aerobic aquatic	N/A	N/A
			Anaerobic aquatic	N/A	N/A
			Field studies	Not provided	Not provided

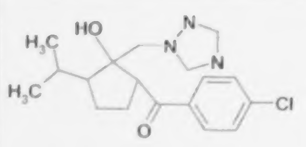
Code	Chemical name	Chemical structure	Study	Max % Applied radioactivity	% radioactivity at study end (study length)
KNF-317-M-11	(1R , 2S, 5S)-2-(4-chlorobenzoyl)-5-isopropoyl-1 - (1H-1,2,4-triazol- 1-ylmethyl)cyclopentanol		Aerobic soil	**Study 1** 14C-Triazole: 3.2% (90) 14benzyl: 3.2% (122) **Study 2 (20°C)** 2.6% (90) 4.0% (60) 4.7% (90) **(10°C)** 3.9 % (120)	**Study 1** 14C-Triazole: 2.6% (230) 14benzyl: 3.1% (230) **Study 2 (20°C)** 1.6% (120) 1.6% (120) 1.7% (120) **(10°C)** 3.9 % (120)
			Anaerobic soil	14C-Triazole: 0.7% (0 and 37) 14Cbenzyl: 0.9 % (97)	14C-Triazole: 0.6% (120) 14Cbenzyl: 1.1% (120)
			Soil photolysis	N/A	N/A
			Aqueous photolysis	Not provided	Not provided
			Hydrolysis	Not provided	Not provided
			Aerobic aquatic	N/A	N/A
			Anaerobic aquatic	N/A	N/A
			Field studies	Not provided	Not provided

Table 15 Toxicity to Non-Target Species

Organism	**Exposure**	**Test substance**	**Endpoint value**	**Degree of toxicity**[a]	**Reference**
Terrestrial organisms					
Invertebrates	Not required for the current use pattern. May be required if future label expansion.				
Birds					
Bobwhite quail	Acute		LD_{50} = 962 mg a.i./kg bw		1368748
	8-d Dietary	ipconazole	LC_{50} > 5710 mg/kg diet	Practically non-toxic	1368752
	Reproduction	ipconazole	NOEC 48.5 mg/kg diet for reproductive effects (survivors/# of hatchlings, survivors/# of eggs set, hatchling survival/pen, and survivors/# of live embryos		1368757
Mallard duck	Acute	N/A	N/A	N/A	
	8-d Dietary	ipconazole	LC_{50} > 5710 mg/kg diet	Practically non-toxic	1368754
	Reproduction	ipconazole	NOEC 197 mg/kg diet for all reproductive effects		1368760

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Mammals					
Rat	Acute	ipconazole	LD_{50} = 888 mg a.i./kg bw (♀)	Moderate toxicity	819497
	Dietary	No test applicable to the EAD was conducted.			
	Reproduction	ipconazole	Parental NOAEL = 2.2 mg a.i./kg bw/d (♂) (body weight and weight gain) Parental NOAEL = 2.6 mg a.i./kg bw/d (♀) (decreased body weight gain, decreased food consumption) Reproductive NOAEL = 22 mg a.i./kg bw/d (♂) NOAEL = 8.4 mg a.i./kg bw/d (♀) (decreased ovary weight, increased duration regular oestrus cycle, decreased total/mean # implantation sites, decreased total offspring #/mean total litter size) Offspring NOAEL = 2.0 mg a.i./kg bw/d (♂ and ♀) (decreased body weight gain)		1368634 to 1368640
	Developmental	ipconazole	Maternal and developmental NOAEL = 10 mg a.i./kg bw/d (decreased body wieght gain and decrease feeding for maternal, decreased fetal weight for developmental)		1368643
Mouse	Acute	ipconazole	LD_{50} = 468 mg a.i./kg bw (♀) LD_{50} = 537 mg a.i./kg bw (♂)	Moderate toxicity	1368575
	Dietary	No test applicable to the EAD was conducted.			
	Reproduction	No test applicable to the EAD was conducted.			
Vascular plants	Not required.				
Aquatic organisms					
Freshwater species					
Daphnia magna	Acute	ipconazole	48-h LC_{50} =1.7 mg/L	Moderately toxic	819508, 874160
	Chronic	ipconazole	21-d NOEC = 0.0109 mg/L (adult growth)		1368739
Rainbow trout	Acute	ipconazole	96-h LC_{50} = 1.5 mg/L	Moderately toxic	819509
Bluegill sunfish	Acute	ipconazole	96-h LC_{50} = 1.3 mg/L	Moderately toxic	1368744
Fathead minnow	Early life stage	ipconazole	28-d NOEC = 0.00018 mg/L (post-hatch survival)		1368741

Table 16 Screening Level Risk Assessment on Birds and Mammals: Consuming Corn Seed, Based on NOELs

Organism and body weight	Toxicity test exposure	Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint[1]		Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day		Risk Quotient[4]
		Screening Level Toxicity Endpoint	# seeds to reach toxicity endpoint	Screening level EDE[2]	EDE[3]	Bolded where RQ ≥ LOC (≥1.0)
small bird (20 g)	Acute oral-single dose	LD_{50} ÷ 10 = 96.2 mg a.i./kg bw	202.5 seeds/d	5.1 × 2.63 seeds/g	13.4 seeds/day	0.066
	5-day dietary	5-day LD_{50} ÷ 10 = 147.5 mg a.i./kg bw/d	310.5 seeds/d	5.1 × 2.63 seeds/g	13.4 seeds/day	0.043
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	8.76 seeds/d	5.1 × 2.63 seeds/g	13.4 seeds/day	**1.53**
medium bird (100 g)	Acute oral-single dose	LD_{50} ÷ 10 = 96.2 mg a.i./kg bw	1012.5 seeds	19.9 × 2.63 seeds/g	52.3 seeds/day	0.052
	5-day dietary	5-day LD_{50} ÷ 10 = 147.5 mg a.i./kg bw/d	1552.6 seeds/d	19.9 × 2.63 seeds/g	52.3 seeds/day	0.034
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	43.8 seeds/d	19.9 × 2.63 seeds/g	52.3 seeds/day	**1.19**
large bird (1000 g)	Acute oral-single dose	LD_{50} ÷ 10 = 96.2 mg a.i./kg bw	10126 seeds	58.1 × 2.63 seeds/g	152.8 seeds/day	0.015
	5-day dietary	5-day LD_{50} ÷ 10 = 147.5 mg a.i./kg bw/d	15526 seeds/d	58.1 × 2.63 seeds/g	152.8 seeds/day	0.0098
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	437.9 seeds/d	58.1 × 2.63 seeds/g	152.8 seeds/day	0.35
small mammal (15 g)	Acute oral-single dose	LD_{50} ÷ 10 = 46.8 mg a.i./kg bw	73.9 seeds/d	2.2 × 2.63 seeds/g	5.8 seeds/day	0.078
	X-day dietary	No test applicable to the EAD was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 3.47 seeds/d Reproductive: 13.3 seeds/d Offspring: 3.16 seeds/d	2.2 × 2.63 seeds/g	5.8 seeds/day	**Parental: 1.67** Reproductive: 0.44 **Offspring: 1.8**
	Developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	15.8 seeds/d	2.2 × 2.63 seeds/g	5.8 seeds/day	0.37

Organism and body weight	Toxicity test exposure	Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint[1]		Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day		Risk Quotient[4]
		Screening Level Toxicity Endpoint	**# seeds to reach toxicity endpoint**	**Screening level EDE[2]**	**EDE[3]**	**Bolded where RQ ≥ LOC (≥1.0)**
medium mammal (35 g)	Acute oral-single dose	LD_{50} ÷ 10 = 46.8 mg a.i./kg bw	172 seeds/d	4.5 × 2.63 seeds/g	11.8 seeds/day	0.068
	X-day dietary	No test applicable to the EAD was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 8.1 seeds/d Reproductive: 30.9 seeds/d Offspring: 7.37 seeds/d	4.5 × 2.63 seeds/g	11.8 seeds/day	**Parental: 1.46** Reproductive: 0.38 **Offspring: 1.6**
	Developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	36.8 seeds/d	4.5 × 2.63 seeds/g	11.8 seeds/day	0.32
large mammal (1000 g)	Acute oral-single dose	LD_{50} ÷ 10 = 46.8 mg a.i./kg bw	4926 seeds	68.7 × 2.63 seeds/g	180.7 seeds/day	0.037
	X-day dietary	No test applicable to the PMRA was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 231.6 seeds/d Reproductive: 884.2 seeds/d Offspring: 210.5 seeds/d	68.7 × 2.63 seeds/g	180.7 seeds/day	Parental: 0.78 Reproductive: 0.2 Offspring: 0.86
	developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	1053 seeds/d	4.5 × 2.63 seeds/g	11.8 seeds/day	0.17

[1] Toxicity(# seeds or # granules (per day)) = Toxicity Dose (mg a.i./kg bw; or mg a.i./kg bw/day) × bw (kg) ÷ mg a.i./seed (or granule)

[2] Food Ingestion Rates (FIR) × seeds/g. for FIR (Nagy,1987):
BIRDS - For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used.
Passerine Equation (body weight ≤ 200 g): FIR (g dry weight/day) = 0.398(bw in g)$^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(bw in g)$^{0.651}$
MAMMALS - The all mammals equation was used.
All mammals Equation: FIR (g dry weight/day) = 0.235(bw in g)$^{0.822}$

[3] EDE(# seeds or # granules/day)= FIR(g dw/day) × (# seeds or # granules)/g

[4] RQ = EDE/Toxicity

Table 17 Screening Level Risk Assessment on Birds and Mammals: Consuming Wheat Seed, Based on NOELs

Organism and body weight	Toxicity test exposure	Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint[1]		Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day		Risk Quotient[4]
		Screening Level Toxicity Endpoint	# seeds to reach toxicity endpoint	Screening level EDE[2]	EDE[3]	Bolded where RQ ≥ LOC (≥1.0)
small bird (20 g)	Acute oral-single dose	$LD_{50} \div 10 =$ 96.2 mg a.i./kg bw	2960 seeds/d	5.1 × 23.2 seeds/g	118 seeds/day	0.04
	5-day dietary	5-day $LD_{50} \div 10 =$ 147.5 mg a.i./kg bw/d	4539 seeds/d	5.1 × 23.2 seeds/g	118 seeds/day	0.03
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	128 seeds/d	5.1 × 23.2 seeds/g	118 seeds/day	0.92
medium bird (100 g)	Acute oral-single dose	$LD_{50} \div 10 = 96.2$ mg a.i./kg bw	14800 seeds/d	19.9 × 23.2 seeds/g	462 seeds/day	0.03
	5-day dietary	5-day $LD_{50} \div 10 = 147.5$ mg a.i./kg bw/d	22692 seeds/d	19.9 × 23.2 seeds/g	462 seeds/day	0.02
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	640 seeds/d	19.9 × 23.2 seeds/g	462 seeds/day	0.72
large bird (1000 g)	Acute oral-single dose	$LD_{50} \div 10 = 96.2$ mg a.i./kg bw	148000 seeds/d	58.1 × 23.2 seeds/g	1348 seeds/day	0.009
	5-day dietary	5-day $LD_{50} \div 10 = 147.5$ mg a.i./kg bw/d	226923 seeds/d	58.1 × 23.2 seeds/g	1348 seeds/day	0.006
	Reproduction	NOEL = 4.16 mg a.i./kg bw/d	6400 seeds/d	58.1 × 23.2 seeds/g	1348 seeds/day	0.21
small mammal (15 g)	Acute oral-single dose	$LD_{50} \div 10 = 46.8$ mg a.i./kg bw	1080 seeds/d	2.2 × 23.2 seeds/g	51 seeds/day	0.05
	X-day dietary	No test applicable to the PMRA was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 51 seeds/d Reproductive: 194 seeds/d Offspring: 46 seeds/d	2.2 × 23.2 seeds/g	51 seeds/day	**Parental: 1.0** Reproductive: 0.26 **Offspring: 1.1**
	Developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	231 seeds/d	2.2 × 23.2 seeds/g	51 seeds/day	0.22

Organism and body weight	Toxicity test exposure	Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint[1]		Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day		Risk Quotient[4]
		Screening Level Toxicity Endpoint	# seeds to reach toxicity endpoint	Screening level EDE[2]	EDE[3]	Bolded where RQ ≥ LOC (≥1.0)
medium mammal (35 g)	Acute oral-single dose	LD_{50} ÷ 10 = 46.8 mg a.i./kg bw	2520 seeds/d	4.5 × 23.2 seeds/g	104 seeds/day	0.04
	X-day dietary	No test applicable to the PMRA was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 119 seeds/d Reproductive: 452 seeds/d Offspring: 108 seeds/d	4.5 × 23.2 seeds/g	104 seeds/day	Parental: 0.87 Reproductive: 0.23 Offspring: 0.96
	Developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	538 seeds/d	4.5 × 23.2 seeds/g	104 seeds/day	0.19
large mammal (1000 g)	Acute oral-single dose	LD_{50} ÷ 10 = 46.8 mg a.i./kg bw	72000 seeds/d	68.7 × 23.2 seeds/g	1594 seeds/day	0.02
	X-day dietary	No test applicable to the PMRA was conducted.				
	Multi-generation reproduction	Parental NOEL = 2.2 mg a.i./kg bw/d Reproductive NOEL = 8.4 mg a.i./kg bw/d Offspring NOEL = 2.0 mg a.i./kg bw/d	Parental: 3385 seeds/d Reproductive: 12923 seeds/d Offspring: 3077 seeds/d	68.7 × 23.2 seeds/g	1594 seeds/day	Parental: 0.47 Reproductive: 0.12 Offspring: 0.52
	Developmental	Maternal and developmental NOEL = 10 mg a.i./kg bw/d	15385 seeds/d	4.5 × 23.2 seeds/g	1594 seeds/day	0.1

[1] Toxicity(# seeds or # granules (per day)) = Toxicity Dose (mg a.i./kg bw; or mg a.i./kg bw/day) × bw (kg) ÷ mg a.i./seed (or granule)

[2] Food Ingestion Rates (FIR) × seeds/g. for FIR (Nagy,1987):
BIRDS - For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used.
Passerine Equation (body weight ≤ 200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{bw in g})^{0.651}$
MAMMALS - The all mammals equation was used.
All mammals Equation: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$

[3] EDE(# seeds or # granules/day)= FIR(g dw/day) × (# seeds or # granules)/g

[4] RQ = EDE/Toxicity

Table 18 Refined Risk Assessment for Small and Medium Sized Birds and Mammals: Consuming Corn Seed, Based on LOELs

Organism and body weight	**Toxicity test exposure**	**Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint**[1]		**Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day**		**Risk Quotient**[4]
		Screening Level Toxicity Endpoint	**# seeds to reach toxicity endpoint**	**Screening level EDE**[2]	**EDE**[3]	**Bolded where RQ ≥ LOC (≥1.0)**
Small bird (20 g)	Reproduction	LOEL = 8.24 mg a.i./kg bw/d	17.4 seeds/d	5.1 × 2.63 seeds/g	13.4 seeds/day	0.77
Medium bird (100 g)	Reproduction	LOEL = 8.24 mg a.i./kg bw/d	87 seeds/d	19.9 × 2.63 seeds/g	52.3 seeds/day	0.60
small mammal (15 g)	Multi-generation reproduction	Parental LOEL = 7.2 mg a.i./kg bw/d Reproductive LOEL = 25.5 mg a.i./kg bw/d Offspring LOEL = 8 mg a.i./kg bw/d	Parental: 11.4 seeds/d Reproductive: 40.3 seeds/d Offspring: 12.6 seeds/d	2.2 × 2.63 seeds/g	5.8 seeds/day	Parental: 0.51 Reproductive: 0.14 Offspring: 0.46
medium mammal (35 g)	Multi-generation reproduction	Parental LOEL = 7.2 mg a.i./kg bw/d Reproductive LOEL = 25.5 mg a.i./kg bw/d Offspring LOEL = 8 mg a.i./kg bw/d	Parental: 26.5 seeds/d Reproductive: 94.1 seeds/d Offspring: 29.5 seeds/d	4.5 × 2.63 seeds/g	11.8 seeds/day	Parental: 0.45 Reproductive: 0.13 Offspring: 0.37

[1] Toxicity(# seeds or # granules (per day)) = Toxicity Dose (mg a.i./kg bw; or mg a.i./kg bw/day) × bw (kg) ÷ mg a.i./seed (or granule)

[2] Food In gestion Rates (FIR) × seeds/g. for FIR (Nagy,1987):
BIRDS - For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used.
Passerine Equation (body weight * 200 g) : FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight > 200 g) : FIR (g dry weight/day) = $0.648(\text{bw in g})^{0.651}$
MAMMALS - The all mammals equation was used.
All mammals Equation: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$

[3] EDE(# seeds or # granules/day)= FIR(g dw/day) × (# seeds or # granules)/g

[4] RQ = EDE/Toxicity

Table 19 Refined Risk Assessment for Small Mammals: Consuming Wheat Seed, Based on LOELs

Organism and body weight	Toxicity test exposure	Toxicity Endpoint expressed as: # seeds or # granules to reach toxicity endpoint[1]		Exposure: Estimated Daily Exposure (EDE) expressed as: # seeds consumed/day		Risk Quotient[4]
		Screening Level Toxicity Endpoint	# seeds to reach toxicity endpoint	Screening level EDE[2]	EDE[3]	Bolded where RQ ≥ LOC (≥1.0)
small mammal (15 g)	Multi-generation reproduction	Parental LOEL = 7.2 mg a.i./kg bw/d Reproductive LOEL = 25.5 mg a.i./kg bw/d Offspring LOEL = 8 mg a.i./kg bw/d	Parental: 167 seeds/d Reproductive: 590 seeds/d Offspring: 184 seeds/d	2.2 × 23.2 seeds/g	51 seeds/day	Parental: 0.31 Reproductive: 0.08 Offspring: 0.28

[1] Toxicity(# seeds or # granules (per day)) = Toxicity Dose (mg a.i./kg bw; or mg a.i./kg bw/day) × bw (kg) ÷ mg a.i./seed (or granule)

[2] Food Ingestion Rates (FIR) × seeds/g. for FIR (Nagy,1987):
BIRDS - For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used.
Passerine Equation (body weight ≤ 200 g): FIR (g dry weight/day) = 0.398(bw in g)$^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(bw in g)$^{0.651}$
MAMMALS - The all mammals equation was used.
All mammals Equation: FIR (g dry weight/day) = 0.235(bw in g)$^{0.822}$

[3] EDE(# seeds or # granules/day)= FIR(g dw/day) × (# seeds or # granules)/g

[4] RQ = EDE/Toxicity

Table 20 Screening Level Risk Assessment on Aquatic Organisms

Organism	Exposure	Endpoint value	EEC	RQ	≥ LOC (1.0)
Freshwater species					
Daphnia magna	Acute	48 hour LC_{50} = 1.7 mg a.i./L ÷ 2 = 0.85 mg a.i./L	0.00034 mg a.i./L	0.0004	no
	Chronic	0.0109 mg a.i./L	0.00034 mg a.i./L	0.03	no
Rainbow trout	Acute	96 hour LC_{50} = 1.5 mg a.i./L ÷ 10 = 0.15 mg a.i./L	0.00034 mg a.i./L	0.002	no
	Chronic				
Bluegill sunfish	Acute	96 hour LC_{50} = 1.3 mg a.i./L ÷ 10 = 0.13 mg a.i./L	0.00034 mg a.i./L	0.003	no
Fathead minnow	Chronic	NOEC = 0.00018 mg a.i./L	0.00034 mg a.i./L	1.9	yes
Amphibian (using most sensitive fish endpoints)	Acute	96 hour LC_{50} = 1.3 mg a.i./L ÷ 10 = 0.13 mg a.i./L	0.0018 mg a.i./L	0.01	no
	Chronic	NOEC = 0.00018 mg a.i./L	0.0018 mg a.i./L	10	yes

Table 21 Risk to Fish and Amphibians at the Tier I Risk Assessment Level

Organism	Exposure	Endpoint value	EEC	RQ	≥ LOC (1.0)
Freshwater species					
Fathead minnow	Chronic	NOEC = 0.00018 mg a.i./L	0.000059 mg a.i./L	0.33	no
Amphibian (using most sensitive fish endpoints)	Chronic	NOEC = 0.00018 mg a.i./L	0.000061 mg a.i./L	0.34	no

Table 22 Alternative Fungicide Seed Treatment Products Registered on Small Grain Cereals

Product	Active Ingredient(s)	Classification	Crops
Vitaflo-280 (11423)	Carbathiin + thiram	7, M	Wheat, barley, oats, rye, triticale
Raxil T (27566)	Tebuconazole + thiram	3, M	Wheat, barley, oats
Raxil MD (27692)	Tebuconazole + metalaxyl	3, 4	Wheat, barley, oats
Baytan 30 (24677)	Triadimenol	3	Wheat, barley
Dividend XL (25778), Dividend XL RTA (25777)	Difenoconazole + metalaxyl	3, 4	Wheat, barley, oats, rye, triticale
Charter (26455)	Triticonazole	3	Wheat, barley, oats
Maxim 480 FS (27001)	Fludioxonil	11	Wheat, barley, oats, rye, triticale
AGSCO DB-Red L	Maneb	M	Wheat, barley, oats, rye
Gemini (27826)	Triticonazole + thiram	3, M	Wheat, barley, oats

Table 23 Alternative Fungicide Seed Treatment Products Registered on Corn

Product	Active Ingredient(s)	Classification
Agrox CD (26957) Agrox FL (12028) Caption CT (26987) Captan 400 (22819)	Captan	M
DCT (14986)	Captan + Thiophanate methyl	M, 1
Vitaflo-280 (11423)	Carbathiin + Thiram	7, M
Maxim 480 FS (27001)	Fludioxonil	11
Maxim XL (27071)	Fludioxonil + Metalaxyl	11, 4
Dynasty 100 FS (28394)	Azoxystrobin	11
Dividend XL (25778), Dividend XL RTA (25777)	Difenoconazole + Metalaxyl	3, 4
Thiram 75WP (27556)	Thiram	M
Dithane M-45 (27616)	Mancozeb	M

Table 24 Rancona Apex Fungicide Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Crop	Rate (mL/100 kg seed)	Disease Claim	Supported/Unsupported
Barley	325	**Diseases Controlled:** Seed rot caused by *Aspergillus* spp., *Penicillium* spp. Seed rot/pre-emergence damping off, post-emergence damping-off and seedling blight (seed- and soil-borne *Fusarium* spp. and *Cochliobolus sativus*) Covered smut (*Ustilago hordei*) False loose smut (*U. nigra*) Leaf stripe (*Pyrenophora graminea*) **Diseases Suppressed:** Common root rot (*Cochliobolus sativus*) Crown and foot rot (*Fusarium* spp.)	Supported as proposed.
	325 - 433 Use higher rate for highly infected seed lots.	**Diseases Controlled:** True loose smut (*Ustilago nuda*)	Supported as proposed.
Wheat	325	**Diseases Controlled:** Seed rot caused by *Aspergillus* spp., *Penicillium* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off and seedling blight (seed- and soil-borne *Fusarium* spp. and *Cochliobolus sativus*) Loose smut (*Ustilago tritici*) Common bunt (*Tilletia tritici, T. laevis*) **Diseases Suppressed:** Common root rot (*Cochliobolus sativus*) Crown and foot rot (*Fusarium* spp.)	Supported as proposed.
Oats	325	**Diseases Controlled:** Seed rot caused by *Aspergillus* spp., *Penicillium* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off and seedling blight (seed- and soil-borne *Fusarium* spp. and *Cochliobolus sativus*) Loose smut (*Ustilago avenae*) Covered smut (*U. kolleri*) **Diseases Suppressed:** Common root rot (*Cochliobolus sativus*) Crown and foot rot (*Fusarium* spp.)	Supported as proposed.

Crop	Rate (mL/100 kg seed)	Disease Claim	Supported/Unsupported
Rye	325	**Diseases Controlled:** Seed rot caused by *Aspergillus* spp., *Penicillium* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off and seedling blight (seed- and soil-borne *Fusarium* spp. and *Cochliobolus sativus*) **Diseases Suppressed:** Common root rot *(Cochliobolus sativus)* Crown and foot rot (*Fusarium* spp.)	Supported as proposed.
Triticale	325	**Diseases Controlled:** Seed rot caused by *Aspergillus* spp., *Penicillium* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off and seedling blight (seed- and soil-borne *Fusarium* spp. and *Cochliobolus sativus*) **Diseases Suppressed:** Common root rot *(Cochliobolus sativus)* Crown and foot rot (*Fusarium* spp.)	Supported as proposed.

Table 25 Rancona 3.8 FS Fungicide and Vortex FL Seed Treatment Fungicide Use (label) Claims for Corn Proposed by Applicant and Whether Acceptable or Unsupported

Disease Claim	Rate (mL/100 kg seed)	Supported/Unsupported
Diseases Controlled: Seed rot/pre-emergence damping-off caused by seed-borne *Aspergillus* spp., *Cladosporium* spp., seed-borne *Fusarium* spp., and *Rhizopus* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off and seedling blight caused by soil-borne *Fusarium* spp. Seed rot/pre-emergence damping-off, post-emergence damping-off caused by soil-borne *Rhizoctonia solani* Seedling blight caused by seed-borne *Fusarium* spp.	5.6	Supported as proposed.
Diseases Suppressed Seed rot/pre-emergence damping-off caused by seed-borne *Penicillium* spp.	5.6	Supported as proposed.

Table 26 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Are criteria met?	Transformation Products Are criteria met?
CEPA toxic or CEPA toxic equivalent*	Yes		Yes	
Predominantly anthropogenic**	Yes		Yes	
Persistent	Persistent in one of the following media:		Yes: Persistent in soil	
	Soil	Half-life ≥ 182 days	Half-life = 180 to 590 days	
	Water	Half-life ≥ 182 days	Half-life not available	
	Sediment	Half-life ≥ 365 days	Half-life not available	
	Air	Half-life ≥ 2 days or evidence of long range transport	volatilisation is not an important route of dissipation	
Bioaccumulative	The log L_{OW} and/or BCF and/or BAF are preferred over log K_{ow}.		Not bioaccumulative	No: log K_{ow} < active ingredient log K_{ow}
	Log $K_{ow} \geq 5$		cc isomer: 4.65 ct isomer: 4.44	
	BCF ≥ 5000		92 to 320	
	BAF ≥ 5000		not available	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1.	No, does not meet TSMP Track 1.

* All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

** The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

A number of the specified Canadian MRLs are the same as those in the US In 4 cases, the MRL differs from the tolerance established in the US (40 CFR Part 180).

Table 1 Difference Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Cotton, gin byproducts	—	0.01	Not reviewed by Codex
Cotton, undelinted seed	—	0.01	
Grain, cereal, forage, fodder and straw, group 16, except rice	—	0.01	
Soybean, forage	—	0.01	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

Appendix III Crop Groups: Numbers and Definitions

Crop Group Number	Name of the Crop Group	Commodity
15	Cereal Grains	Barley Buckwheat Field corn Sweet corn kernels plus cob with husks removed Pearl millet Proso millet Oats Popcorn grain Rye Sorghum Teosinte Triticale Wheat
6C	Dried shelled pea and bean (except soybean) subgroup	Grain lupin Dry kidney beans Dry lima beans Dry navy beans Dry pink beans Dry pinto beans Dry tepary beans Dry beans Dry adzuki beans Dry blackeyed peas Dry catjang seed Dry moth beans Dry mung beans Dry rice beans Dry southern peas Dry urd beans Dry broad beans Dry chickpeas Dry guar seed Dry lablab beans Dry lentils Dry field peas Dry pigeon peas

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1398148	3.1.1 Applicants Name and Office Address, DACO: 3.1.1
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4.0 Value

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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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